* 1.   
  Kresge 502 Cart: Welcome to the epidemiology of cancer. My name is Laura Lai Moochie. I actually don't know how long I've been teaching this class, I should know, I think Ed just told me. Well, he's been teaching it, and but it's been incredible to be part of his team.

0:50

* Kresge 502 Cart: oh, yes, it's this is the 30 first year.

1:09

* Kresge 502 Cart: So but don't worry. We haven't

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* Kresge 502 Cart: many younger people. I do a lot of work in

1:16

* Kresge 502 Cart: Hi Margaret's molecular epidemiology. You'll hear me talk a little bit about prostate cancer, which is a cancer. I do a lot of work on and Ed, yeah, also cancer epidemiologists. I was. I took this discourse and

1:32

* Kresge 502 Cart: 1986,

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* Kresge 502 Cart: and I do mostly cancer epidemiology. With a nutrition focus some frosty but

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* Kresge 502 Cart: more of a color rectal and like gas for intestinal cancers, although it won't be giving the prostate cancer lecture this year. That's yeah. Right. We actually have 2 amazing teaching fellows here. I'm gonna let introduce themselves. So Pauline

2:02

* Kresge 502 Cart: Picky

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* Kresge 502 Cart: and Hi, everyone and Michelle

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* Kresge 502 Cart: kind of delve into a little bit some of the core concepts before that. I always like to start our classes with

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* Kresge 502 Cart: a quiz. And so have people use poll everywhere before. If you haven't. There's 2 ways to access. The first is you can go open up a web browser and type in POLL. [e.com](http://e.com/) backslash, and then my name, Laura Laimuchi, 9, 6. The other way you can do it is if you want. If you want to use your cell phone, you can text the number 37607. And in the.

3:11

* Kresge 502 Cart: you know message, you, you type more alignment G, 9, 6, 6. So that will get you kind of activated. So is everybody on pull everywhere.

3:38

* Kresge 502 Cart: Should I? Does anybody not need a little bit more time?

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* Kresge 502 Cart: Perfect cause? Then I'll go. I'll switch over to the poll everywhere, so we can sort of ask questions.

3:55

* Kresge 502 Cart: And this is not part of the graded assignment. So there's a don't. So don't worry about this. I think it's it's just nice to sort of see where the class is at every every day. So alright. So I'm gonna go over to the

4:07

* Kresge 502 Cart: How do? How do you switch over? Sorry escape. I did a so there we go, perfect

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* Kresge 502 Cart: alright. And

4:28

* Kresge 502 Cart: it was. It was just up a second ago.

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* Kresge 502 Cart: Where is it? Oh, here it is.

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* Kresge 502 Cart: But people have already

4:42

* Kresge 502 Cart: started voting. Okay? Great. So the question, yes, but sorry.

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* Kresge 502 Cart: No, no. Yep. So the question is, you know, each year in the United States, actually, now, it's closer to 2 million people will be diagnosed with some form of cancer. So the question that we're asking you is, what proportion of those cancer diagnoses in the United States do you think are preventable? Meaning, you know what? What

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* Kresge 502 Cart: portion? If you could eliminate all the cancer risk factors, could you actually pre prevent? So is it 7, 2540, or 90? So you can enter what you think is the right answer, and, as you can see, as answers are coming in, and sort of kind of going up and down. So let's give it 5 more seconds.

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* Kresge 502 Cart: 5, 4,

5:36

* Kresge 502 Cart: 3, 2,

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* Kresge 502 Cart: one perfect. So I guess we don't need to really teach this class, because, most of you got the right answer. So in the United States, about 40% of cancer diagnoses are thought to be preventable.

5:42

* Kresge 502 Cart: So we know a lot about how to prevent cancer. So one big challenge. And one thing we'll be talking about here is if we know these risk factors and we'll talk about what the risk factors are or opportunities for prevention. How do we translate that? Why can't we translate or implement those changes in the population? We'll also talk about cancers for which we actually don't know as much about in terms of the epidemiology and areas there for for potential growth. So excellent, fantastic.

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* Kresge 502 Cart: Okay, so we're going to go into the course overview. I already did introductions of all of us.

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* Kresge 502 Cart: I'll I'll start with the course of Jack's, and then you can. Or yeah, once you alright, you would think that we hadn't taught this class before that we're so so there's there's several objectives of of this course. And I think, as I mentioned, we're gonna we're gonna spend a lot of time delving into what are some of the major categories of of what we think are causal factors in the ideology of cancer. And also like what are some

6:32

* Kresge 502 Cart: really interesting hypotheses about? Why cancer occurs. We'll spend some time, both in class in each of the lectures, as well as one of your assignments, is going to be focused more on the descriptive epidemiology of cancer and looking not only in the Us, we really try to have a global focus. Third. And I guess this is really across the lectures, is looking at. What are the populations of people

7:02

* Kresge 502 Cart: for which Ca, a specific cancer may have a higher incidence, a higher mortality. We're gonna weave into the course and today and today and some. And on Thursday spend some time talking about some of the core methodological issues and cancer epidemiology, study, design analysis and bias and then, as I mentioned, for for your group project, you're gonna get an opportunity to work with some of the primary data sources

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* to look at the descriptive epidemiology of cancer.

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* Kresge 502 Cart: Sure, yeah.

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* Kresge 502 Cart: the I think you all have a syllabus. So basically.

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* Kresge 502 Cart: the the course. Like, you know, we're trying to give an overview of concepts like methods and and issues like we, we won't get

8:05

* Kresge 502 Cart: into very like, you know, like statistical methods like this is more of a broad picture

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* Kresge 502 Cart: view of of cancer. And get into a lot of like the descriptive epidemiology. but you know, the focus is really learning to understand the literature from a big picture perspective like how to interpret

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* Kresge 502 Cart: the study. You know, we interpret studies individually, but also in the context of other like

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* Kresge 502 Cart: studies like. so, oh, yeah.

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* Kresge 502 Cart: so so the lectures like W, it's kind of broken up in 2 ways, conceptually like we have some lectures that'll focus on exposures like tobacco obesity infections

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* Kresge 502 Cart: radiation. We, we don't have a lot. Specifically. We used to have a lecture on radiation which is actually interesting topic, even though it doesn't really cause a lot of cancers. But there are a lot of that interesting ways that helps understand how

9:05

* Kresge 502 Cart: how cancers occur, like, you know, like mutations, things like that. But we, we will talk about a little bit for some of the cancers, but we don't have a specific lecture, and then genetics and and then diet also, I I'll I'll be talking about like obesity diet, and can also include physical activity there.

9:22

* Kresge 502 Cart: And then some lectures will be mostly focused on the disease like specifically breast prostate colon liver and pancreatic cancers. And then in in their class assignments, we'll talk about other cancers that that won't have the big lectures, but well, you know, they'll each get at least 15 min of

9:44

* Kresge 502 Cart: of fame for for into some individual cancers. And of course, you know, like what? When we're talking about the exposures, we'll be talking about specific cancers. But that's just the way the lectures will be focused more.

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* Kresge 502 Cart: When, when like, we're talking about tobacco, a lot of it will be on one cancer. So you'll get a lot of one cancer. But we'll also talk about other

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* Kresge 502 Cart: alcohol smoking related alcohol is another thing that you'll you'll get some exposure to alcohol. I mean, I don't mean physical exposure.

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* Kresge 502 Cart: So a in the class format. The classes include presentations by the course instructors, and we have a lot of great guest lectures. And but even though it's a lecture format we actually like and and

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* Kresge 502 Cart: you know, prefer a lot of interaction. So over the years, I've tried to have more time for for people to have discussion. I don't often do a great job in that, but but we'll try to have more, you know. Feel free any time to to raise your hand if the points not clear, or if you wanna make a point so and then also. We'll have some interactive learning

11:00

* Kresge 502 Cart: during the classes which we'll get into later. You have assigned course reading readings. That. You know, it's great

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* Kresge 502 Cart: to to do in advance. II think it would enhance the lecture.

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* Kresge 502 Cart: I live in the real world. We know that not everybody does. All the readings before class. II didn't always do it so have to admit, but but it's it's good if you can. So

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* Kresge 502 Cart: yeah. So so office hours. we'll we'll have a couple of specific off our office hours, that is, are set up around the Descriptive Epidemiology project. We're gonna talk about that in a second and then also before the final quiz. But also you're so welcome. If you wanna meet with us at any time. Just reach out to set up an appointment with either colleen

11:56

* Kresge 502 Cart: Michelle, Ed, or myself, and I think generally we're available immediately after the class until about 4, 4 30. So that's a great time to set some time up to me.

12:20

* Kresge 502 Cart: Yeah, this is the what

12:32

* Kresge 502 Cart: the lectures.

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* Kresge 502 Cart: So the we'll start like the first to lectures. I won't go through every one of these. But just to give you an overview, that laurel, I does a a great job giving sort of the basic concepts of cancer. Epi on some of the descriptive epi and the methods and then next week we'll

12:39

* Kresge 502 Cart: del start delving into the specific topic. So I'll do mostly next week the diet, cancer, obesity, physical activity. And then as you can, you know I will. I won't read all of this. So we have

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* Kresge 502 Cart: a scatter like some cancer, and then infectious diseases. So, and then the in class presentations are, February 20 and the twenty-second. And we'll get into that.

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* Kresge 502 Cart: What? Specifically that means.

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* Kresge 502 Cart: We'll have a class discussion of a paper in February twenty-seventh

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* Kresge 502 Cart: oh, we have February 20 ninth this year. So we have an extra day of work this year. And then, like the final quiz, which always gets people a little anxious. But it's it's only 20% of your grade. So it used to be like 80. So it's people really freaked out but 20 so bad. So and that's on the last day you don't actually have to come, you can do it at all.

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* Kresge 502 Cart: so we'll we'll give you the details

14:07

* Kresge 502 Cart: so so we have, a few different assignments, and and we tried to make them as sort of things that you could take into the real world with you. So one of one of these assignments, which I think we've gotten great feedback on is doing sort of a mock journal critique. So it's learning how being a peer reviewer for a medical journal. So we'll give you some guidelines on our approach of how to look through

14:12

* Kresge 502 Cart: an article and provide, you know, constructed both positive and suggestive feedback. For the authors. It's meant to be short. And again. We'll go into a little bit more detail, probably on Thursday about this specific assignment, which is due on February 6. And it's actually a really interesting paper. So some of you might have heard of an initiative that the Us. National Institute of Health has started a a new group

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* Kresge 502 Cart: cohort study called the all of Us research program. And so this particular article looks at the association between air quality and the risk of cancer using all of us study so you're so welcome each to discuss the article come up with. Maybe some of the points themselves, but we want each of you to write up the assignment independently.

15:02

* Kresge 502 Cart: Yes, sure. So the the other assignment.

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* Kresge 502 Cart: which is 35% of your grade is actually actually has like 2 parts, and this is You'll work in small groups and we'll find out later how

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* Kresge 502 Cart: how those are. You'll kind of self select and so it'll be focusing on a descriptive epidemiology of a specific cancer. So you give like a background of you know that it's it's pretty basic descriptive of epidemiology, incidence, you know, differences by like race things like that. And then also, you you pick

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* Kresge 502 Cart: you select the risk factor for that cancer? And you could, you know, you'll discuss with one of us like, what works factor should you pick? And so there's flexibility in that, and then so you'll

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* Kresge 502 Cart: listed. There are the cancers for this year, so it's blad, so you only so you'll be in one of these cancers, will be a 1 one of the groups. So bladder and the metro ovarian.

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* Kresge 502 Cart: sophocus, kidney glioma like brain melanoma, gastric and testicular cancer. So we're actually doing all of those. Yeah. So and then there's 2 graded components one is the individual where you can read it. So so you'll write up, you know, to short 2 to 3 pages, double space

16:34

* Kresge 502 Cart: and then that's worth the 15% of your grade. And then there will be like a group presentation. which will do on those 2 days in February you have to 20 and 20 s. So as a group like there's like 4 or 5 in a group you all come up. And you know, you, you decide how you gonna break up the presentation. So each gives, you know, a little component and that, and that will be 20% of your grade.

17:00

* Kresge 502 Cart: And then the also part of the grade is

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* Kresge 502 Cart: another. Anybody can ask questions for each presentation. But there's a group that

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* Kresge 502 Cart: is so. For example, like, let's say, the endometrial group is presenting. And then, like the kidney group

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* Kresge 502 Cart: leads to questions. So so.

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* Kresge 502 Cart: yeah, yeah, and actually, so, just so would to sign up for the cancers. You can start thinking already. Now which cancer would be most you're interested in exploring. We'll set it up in in canvas as a way to organ. And so when do you think we should launch that? Okay, okay, perfect.

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* Kresge 502 Cart: So the

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* Kresge 502 Cart: great. So so one of the other assignments again, and thinking about like some real practical things that you can take away from this class is learning. How do you write a letter to the editor? So oftentimes you'll read a public health or medical journal article that's really interesting. And you'd like to respond in a way to either

18:17

* Kresge 502 Cart: highlight. One or 2 specific issues that the paper raise, maybe think about where you might wanna take the paper in a different direction. And so this is going to be a mock letter to the editor, editor and then also, we're gonna have an in person discussion altogether on this paper. So again, this this assignment actually has 2 parts the first will be the in class discussion, which will take place on February twenty-seventh. We'll take about

18:37

* Kresge 502 Cart: I think. Probably 45 to 15 min in total. First, we'll have you in this classroom, break up into small groups together with your neighbors, and just kind of talk through some of the issues. Secondly, we'll all come together with the 4 of us, and really kind of go through. And it's a really interesting paper by Gilbert Welch, who's based on women's hospital and Doctor Day thinking about

19:02

* Kresge 502 Cart: you know, how does cancer screening save lives? So it's a really interesting perspective, perhaps a little controversial, but we'll have a really, I think this is a nice paper also to bring in the concept of of screening into cancer epidemiology. So we'll have the discussion. And some people may not feel as comfortable raising points in class. So we also have. We'll have

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* on of a canvas board, not looking for people to make comments there as well, and then secondly, you'll actually write a very short 500 word letter to the editor in response to this article, and you can work on your own, or if you want to work with a total of 3 authors altogether, including yourself. You can do that as well. That will count for 15.

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* Kresge 502 Cart: And then the final quiz.

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* Kresge 502 Cart: it's all there. Yeah, yes. So you'll have 90 min, and usually we, we try to make it that 90 min should be more than enough but sometimes people say that, but usually it is so and so so you're so you can do it at home or any place. And then I guess it's set up that like once you start.

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* Kresge 502 Cart: you have 90 min. And then II don't know how this tech stuff works. But

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* Kresge 502 Cart: that's it. Yeah, yeah. So you can basically schedule anytime from 9 in the morning on March seventh. All the way through Saturday, March ninth. Yeah, it's 90, continued continuous minutes. True fall short answers multiple choice. You can use class notes, presentations any related merit materials, but it really should be your own work

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* Kresge 502 Cart: before, like the last week, will usually have like a a session like a ta session that you're welcome to? Questions.

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* Kresge 502 Cart: Good.

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* Kresge 502 Cart: Yeah. Question. It sets up to 105. What? Oh, no, this is because this is wrong. This slide is wrong, but not that. Yup. I apologize. It's only 20. We did make changes. I apologize, but very, very thank you for keeping an eye on that. Yeah.

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* Kresge 502 Cart: but on the syllabus it should be correct. Yep.

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* Kresge 502 Cart: see if we haven't noticed that you could have got 5.

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* Kresge 502 Cart: Okay, so generative. AI, so

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* Kresge 502 Cart: so in this particular class, we don't want tools such as chat Gbt, or growerly,

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* Kresge 502 Cart: and using text that's produced by this as part of this course, the assignments really should be written by you in your own words, that reflect your thoughts, and the your understanding of of the content. If you if you feel like you, wanna use it these kind of tools to check grammar spelling that is acceptable. But if you are going to be using it, you should let us know it should be appropriately cited, as it's as you should, otherwise it would be considered

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* Kresge 502 Cart: plagiarism, and we understand that this is a rapidly evolving field in different classes are using generative AI in different ways. But this is the approach that we're gonna be taking for this class.

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* Kresge 502 Cart: So any any questions about the assignments? Or oh, I should say also regarding

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* Kresge 502 Cart: the use of zoom again, we understand that. And there's extenuating circumstances. People may not be able to be in class. We really do hope, though. I think this class is successful because people are here discussing breakout sessions. So. But if things come up and you do need to miss a class or take part in zoom, please just let us know in advance. But any questions about the assignments, or

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* Kresge 502 Cart: what's that?

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* Kresge 502 Cart: Anything else to add?

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* Kresge 502 Cart: Pencil?

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* Kresge 502 Cart: Okay, great, excellent. Well, we'll get started with

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* Kresge 502 Cart: sort of the first part of of the actual lecture, talking about cancer coughs up. So first in terms of what the goals of the lecture today. I think there's so many interesting landmark discoveries that we've made in cancer epidemiology and how

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* Kresge 502 Cart: one those were discovered. And then how long it might take before those initial observations get translated into saying, yes, this is a causal factor. Thinking about that. History, I think, is really interesting. We'll give a really brief overview of the pathology and biology of cancer. And for people who feel like they want to read up more. We have some recommended readings and a book. Chapter. So we'll be talking also

23:49

* about some of the key molecular and genetic features, although I think actually, most of that is probably going to be on Thursday, and then also in Thursday, will be going into more of the actual methodologic concepts and cancer epidemiology. So what is what is cancer. So the the word cancer comes from the Greek word carcinoma for for crab. And this is based on the fact that

24:14

* Kresge 502 Cart: sometimes breast cancer lesions. Can be seen on the surface of the skin and the the appendages going out look like they're reading like a like a crab. It really is a diverse family of diseases, and it can arise in almost every cell of the body.

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* Kresge 502 Cart: They can be a solid tumor or in non solid leukemia.

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* Kresge 502 Cart: and while it kind of rise in almost every cell type, there's considerable variability in the incidence, prevalence, and mortality of these cancers, and and one really striking example, I think, is, is the prostate which is

25:00

* Kresge 502 Cart: again, you'll you'll you'll hear about this in a lecture. But prostate is the most commonly diagnosed cancer in in men or people with prostate in a hundred countries around the world. In including of the United States, however, the structures adjacent to the prostate the seminal vessels. You almost never see a primary cancer rising there. So why.

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* Kresge 502 Cart: no, you have this. You have the prostate. It just shakes kind of like a walnut

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* Kresge 502 Cart: like this. And then you have these adjacent to the seminal vesicles. So you know, the lifetime risk in the us is about one in 8. Yeah, you almost never have a cancer that's primarily here. So why is that? What is it? What's leading to that variability. In addition to unique ideology, there's unique opportunities for prevention, prognosis and treatment. And one of the things that we'll get into for some of the malignancies is that even within a single cancer, like breast cancer, colorectal cancer? We can even think of subsets of those

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* those cancers that again, have their own unique factors, based either on molecular characteristics of the tumors or clinical features of the tumors.

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* Kresge 502 Cart: So let's see what, when you signed up for this course.

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* Kresge 502 Cart: what? What were you thinking that cancer epidemiology is?

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* Kresge 502 Cart: What did you think we would be doing this class? So what for? What is cancer? Epidemiology to you?

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* Kresge 502 Cart: Yes, I thought,

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* Kresge 502 Cart: I'll learn more about it. How the cancer is focusing the

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* Kresge 502 Cart: what are the new ways and treatments that

27:00

* and edit?

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* Kresge 502 Cart: What are the different types of cancers. How? What are the risk? Factors that are involved?

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* Kresge 502 Cart: Learn more about different types of studies?

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* Kresge 502 Cart: Yeah. So I think you've had. You've hit on so many great points. So really think about patterns of cancer occurring in different populations, how we might identify the causes and opportunities for prevented. We might not talk as much about treatments specifically, although in some cases, you know, I think some of our lectures and and some of our individuals we talk about like clinically, what is cancer? Look like when it's presented? And what are the treatments for it?

27:14

* Kresge 502 Cart: And then there was something else that you mentioned. Study design web. Exactly. So, thinking about the methods that we use. You know, there's there's you. You all have taken, probably epidemiology intro to to an epidemiology course. Well, thinking about really, specifically, what is it about cancer that might be unique or ways to think about some of these biases confounding study design specific for cancer epidemiology. What about anybody else? Have anything outside of those things that they were thinking of?

27:43

* Kresge 502 Cart: I think that was a great, a great list.

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* Kresge 502 Cart: Yep, perfect.

28:16

* Kresge 502 Cart: So there's there's a great review article called Landmarks in the history of cancer epidemiology. That I pulled from as well as a a book chapter called the Textbook of Cancer Epidemiology, I think. Did we put the book chapter in the Harvard campus? You can. You can take a look at it as well. Alexander Pope and his essay on man

28:19

* Kresge 502 Cart: said, the proper study of mankind is man. I, you know, as an epidemiologist, I think we're very interested in understanding what are the causes of cancer in the population? Of people rather than in mice or other creatures.

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* Kresge 502 Cart: So just some historical perspective. So the use of tobacco. Actually, it was already in 1761 that Dr. John Hill wrote a pamphlet cautioning against the moderate use of snuff. And this is really he. He wrote this article or this pamphlet, really just a few decades after tobacco became popular in London, and before it was combustible, the first, it was actually an oral type of

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* Kresge 502 Cart: tobacco, called snuff and

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* Kresge 502 Cart: What he observed was that in individuals who are regularly using this smokeless tobacco product. There were all sorts of oral lesions and oral cancers that were occurring. This population, so was already back in 1761 that this he made this kind of connection between use of tobacco and risk of cancer. But it actually wasn't until really many centuries later. That it became

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* Kresge 502 Cart: really established that tobacco was a major cause of different cancers. And we'll go into what those cancers are when we talk about the tobacco and cancer lecture. But it was actually the first real epidemiology study was in 1912 looking at a case control study of tobacco and lung cancer. And then

30:01

* Kresge 502 Cart: It was in the 1950 s. That the first prospective cohort says so again, we'll talk on Thursday a little bit. What's the difference between a case control cohort study for cancer epidemiology? But it was in 1950 s. That the epidemiology really solidified one of the big cohort studies was a a cohort of physicians from the Uk which which actually had a very high prevalence of of

30:19

* Kresge 502 Cart: tobacco use showing up and as a cause of lung cancer. But before then there's a lot of pushback from people. Say it's not tobacco. There must be other factors that these people are doing that would cause cancer. And just give you a context. The Us. Congress establish the National Cancer Institute in 1,937.

30:43

* Kresge 502 Cart: So again, first report in 1761, and then it was 1964 before the Us. Surgeon General first came out with its report on smoking and cancer, and then warning labels appeared on cigarettes in the United States in 1965. So another about 25 years later and one of the the former chairs of epidemiology. Here at the Harvard School of Public Health. Demetrius Chicopoulos was really one of the first.

31:01

* Kresge 502 Cart: I think there were 2 parallel articles that came out looking at secondhand smoke so passive exposure to tobacco smoke as a risk factor for lung cancer, and just like it, with primary smoking and lung cancer. There was a lot of push back on that. And again, we'll we'll talk about that now, but now it's it's pretty well established that exposure to secondhand smoking is a risk factor for lung cancer.

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* Kresge 502 Cart: So another historical perspective. So in the eighteenth century there was an Italian doctor, Ramazini, who made the following observation, in a population of nuns they seem to be immune from developing cervical cancer, but had a higher than expected risk of breast cancer.

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* Kresge 502 Cart: What factors might underlie this association? Once you turn to your neighbor for a minute or 2.

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* Kresge 502 Cart: Talk about what you know. What is this? Up observation? What might be done? A link what? Why, none seem to have a much like a basically immune developing cervical cancer, but a higher than expected risk breast cancer, talk with each other, and we'll come back together in a minute.

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* Kresge 502 Cart: Alright. So maybe we will come back together.

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* Kresge 502 Cart: So I'd love to hear people the the thoughts from your discussion. So

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* Kresge 502 Cart: what were something that you talked? We talked a little bit about what might be the common underlying factor. And you're thinking about non potentially not engaging sexual activity which would be protective factor against sort of cancer. But I remember reading somewhere, and I could be totally wrong that pregnancy is actually associated with a lower risk. So it would be beneficial in one way. But detrimental. Yeah, that's exactly right. So

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* Kresge 502 Cart: for in terms of cervical cancer, exposure to human papilloma virus, either 16 or 18 is a necessary, although not sufficient

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* Kresge 502 Cart: cause of cervical cancer. And we'll, you know. So we just because we have it, doesn't have the infection doesn't get cervical cancer but then, on the flip side. There'll be a great discussion about reproductive factors, including a pregnancy. That is the explanation for higher than expected risk of breast cancer. So that's exactly yep. Any other conversations like or points that you want us to raise up about that?

35:38

* Kresge 502 Cart: Yes, they're like social like. They're environment.

36:03

* Kresge 502 Cart: Oh, that's interesting, right? So we could there also. Right? So I age better. P is an important factor for breast cancer. So the younger age of underp is assisted with an increase to breast cancer. So could there be something in their environment that at least makes that link with breast cancer. So that would be interesting to think about as well.

36:11

* Kresge 502 Cart: Great

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* Kresge 502 Cart: so another historical perspective. And and maybe I give those

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* Kresge 502 Cart: punchline here away. But Harold Zarhausen was a virologist, who had originally hypothesized back in 90 s. 74, that cervical cancer might have a a viral ideology. He initially, he didn't. He thought it was related to herpes virus, too. But what he did was then to look at under the microscope. Cervical cancer specimens.

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* and that's where we discovered it was actually human. Papillomavirus, or Hpv. 16 and 18, ultimately received the Nobel Prize in 2,008

37:06

* Kresge 502 Cart: cool

37:16

* Kresge 502 Cart: right? And so just even it was interesting, though, even though they didn't know the exact cause of cervical cancer pap, smears were actually introduced back in the 1940 S, as a way to really detect presence of either

37:18

* Kresge 502 Cart: cervical cancer earlier than it would otherwise before symptoms, or even with with cervical cancer as well as colorectal cancer. There's a pre, the established, pre malignant lesion. That with a high risk of going on to cancer. So you can. Actually, instead of detecting the cancer itself, you can detect the the pre malignant lesion and take it out and prevent

37:34

* cancer from her happening. So it's a really interesting, an important model for early detection of cancer.

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* Kresge 502 Cart: Yeah. So, and then, just in terms of a timeline so the discovery of Hpv. DNA and cancer cervical cancer specimens made in 1983, and then, about 20 years later, a vaccine against Hpv was approved for the prevention of cervical cancer. Unfortunately, despite the fact that the vaccine is quite effective and preventing

38:05

* Kresge 502 Cart: Hpv infection. It's not broadly available to all parts of the world you still have, and we'll talk about in the descriptive epidemiology and looking at cervical cancer around the world, you have some countries with very high incidence and mortality. From cervical cancer, despite the fact that there's prevention and vaccination. So again, thinking, this is in an interesting model where you know a lot about how to prevent the cancer.

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* Kresge 502 Cart: But we haven't been able to implement those prevention strategies equally around the world. And even in the United States across different populations.

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* Kresge 502 Cart: So in terms of occupational exposures, I think really one of the first strong links between occupation and a cancer was made in 1775. Percival Pot was studying

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* Kresge 502 Cart: children who work chimneys sweep so they would go in down the chimneys and clean with a brush. And there's an excess risk of a cancer that otherwise is quite rare, which is cancer of the scrotum. And you know, this is language that was taken from his observations on this, and he said, You know I've never had seen squirrel cancers under the age of puberty.

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* Kresge 502 Cart: which is what one reason that initially thought to have a a venereal cause so sexually transmitted. Infectious cause. He talks a lot about the brutality of working as a chimney sweep, where they had very young children who are small enough to fit down the chimneys. And they were exposed to these. You know, the he actually wasn't exactly sure what they were being exposed to, but made this observation that it was because they were working as a chimney sweep

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* Kresge 502 Cart: that they had this excess risk of scuttle cancers. So but 100 years later I it took, despite this observation, to implement changes in occupational setting to prevent exposure to you know the suit, but really wasn't identified even until another 60 years later. That what the causal agent

40:14

* Kresge 502 Cart: so it was. So it was actually benzo. A pyre in the suit was leading to this excess risk of scroll cancers. So again, you know, it's interesting with with with smoking and lung cancer. Some people pushed up against that hypothesis being true because one smoking wasn't specific to lung cancer, increase the risk of other cancers, but also they said, Well, what is it? What is it

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* Kresge 502 Cart: carcinogen so you don't know with the carcinogen, so you can't say it's a causally associated with the cancer. So it was interesting here to see how long it really took to translate these findings. These observations into identifying the causal agent, and even took 100 years after the first observation, to get preventive measures in place in the occupational setting.

41:04

* Kresge 502 Cart: So, we again, we'll talk about cancer during each of the specific cancers as an inherited disease. So if you looked at

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* Kresge 502 Cart: the risk of any type of cancers, about 30% of cancer incidence is due to inherited genetic causes. And that's evidence that comes from family based studies and twin studies as well.

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* Kresge 502 Cart: so the the one of the first descriptions of family history of cancer was a was done by Paul Broca, who described this very detailed family history from 1,866, where there were this family had a number of breast cancer cases as well as other cancer cases

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* Kresge 502 Cart: occurring and showing. So the the first matriarch of the family was Mrs. D. And the

42:17

* Kresge 502 Cart: dark spot here is breast cancer, and then there are other cancers as well, looks like there was liver cancer in some of the members as well as other malignancy. So it was really an interesting one of the first ways of tracking that people who have a family history with a sibling, a parent who has cancer or at increased risk of cancer themselves. So does having a family history.

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* Kresge 502 Cart: Mean that it's a genetic cause

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* Kresge 502 Cart: or not? Does it have to? So why or why not?

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* Kresge 502 Cart: What's your thinking when you're hearing family history. What? What might be the reason that your family history is.

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* Clara.

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* Kresge 502 Cart: In what way would you say this might be.

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* Kresge 502 Cart: yeah. So I,

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* Kresge 502 Cart: yeah, yeah, exactly. Right. So so the family members may be eating the same food together, so they're exposed to the same diet. Or maybe there's one person smoking the house, so they're all exposed to passive smoking. Or maybe they're just as likely to get screens like if one of them has cancer than the other. So there's there's sort of this shared environmental factor, that part is family history. And then, of course, there is that genetic component

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* Kresge 502 Cart: as well. So we'll talk about this a little bit more detail. On Thursday.

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* Kresge 502 Cart: So another I think really interesting historical perspective. As as Ed was saying that understanding the impact of radiation on the development of cancer has really helped to understand a number of different factors about mutations that occurring about latency. So there was a really interesting study. And there's actually a movie that was made about this about the it was called the Radium Girls.

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* Kresge 502 Cart: So in 1915 to 1929, which was soon after radiation was really first discovered. they would use a form of radium radium, 2 26 to paint the dials of watches so that they would glow in the dark. So

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* Kresge 502 Cart: with us women were recruited to paint these watch styles, and in fact, I think one of the first watch factories was in Waltham, Massachusetts, so familiar, I think that's right. And so they would basically

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* Kresge 502 Cart: So they had a very fine point on the paintbrush, and so they would be painting the numbers on the dial, and then they would point

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* Kresge 502 Cart: the pink brush meeting that would, they would lift the tip of the paint brush to make it really skinny, you know, if you're trying to

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* Kresge 502 Cart: put thread into a needle, you have to kind of get it really small, so they would do the same thing with the paintbrush. And essentially they were ingesting all of this radiation. Well, soon after they saw an excess incidence of fractures of the bone and then ultimately bone cancers. And it was through this perspective that they made the link between one of the links between radiation and cancer.

45:03

* Kresge 502 Cart: So do you think I can play this video? II forgot to see if we could do this

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* Kresge 502 Cart: if I click on this bullet. Okay, perfect. So Robert Weinberg, there's a there's a recommended meeting in the

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* Kresge 502 Cart: on the Harvard campus page

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* Kresge 502 Cart: which was written by Robert Weinberg. About is Hannah and Weiberg about the. And we'll talk about what these are the sort of the the defining features of cancer he's a he's a biologist physician. But I thought it was really this beautiful piece about importance of cancer prevention. So we thought we would play that here.

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* Kresge 502 Cart: So. And one thing we've talked about in prior classes was, what did what did you think about his comment that if we all live long enough

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* Kresge 502 Cart: we'd ultimately all develop cancer. What do you think about that statement?

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* Kresge 502 Cart: Scared? Scary. Yeah. Yeah.

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* Kresge 502 Cart: It's it's interesting. There, there's, you know, in in again, if we look in the United States. About one in 2 people will develop. Then 1, 2 people identify as men are will develop cancer and women's one and 3

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* Kresge 502 Cart: So there's certain people who seem to be immune from cancer. So I'm not. It's interesting to think what Michelle and colleen what you're

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* Kresge 502 Cart: thoughts are. Ed, what your thoughts are about like. Do you think really, that everybody would develop cancer if we lived to 100 2,130 years, or do you think we really are? There are some people who are really immune, or is it really prevention, death from other causes? Right? If you know, if you didn't die of a heart heart attack, or getting hit by a bus would again would be all live to be

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* Kresge 502 Cart: able to develop cancer. Like, put their eyes down.

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* Kresge 502 Cart: cancers that are not lethal prostate cancer.

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* Kresge 502 Cart: Like Van Biden.

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* Kresge 502 Cart: probably 50%. Yeah, card

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* Kresge 502 Cart: chances are, let's

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* Kresge 502 Cart: that's interesting. Yeah.

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* Kresge 502 Cart: yeah. So what? What that is referring to is a series of what we call autopsy studies. So these are looking at the tissues of people who die of many different causes other than cancer to see if you can see evidence of cancer. And so it goes to this idea of sort of what we call almost like pseudo cancer. Truly cancer, right? It has all the features of what you say is cancer. But it didn't come

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* Kresge 502 Cart: to light anytime while the person was alive. So they died with the cancer, not from the cancer. So that that's an interesting point. Yes, yeah.

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* Kresge 502 Cart: II actually, really. And I think, really, it's really matters how you define cancer. I mean.

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* Kresge 502 Cart: there are certain kinds of cancers, or maybe called by some 3 malignant status. I mean.

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* Kresge 502 Cart: I'm a so in our world, we have all kind of stays that we just discovered in the last couple of years that

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* Kresge 502 Cart: we have the vast majority of older patients have mutations in their DNA and and

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* Kresge 502 Cart: these are with them in a very high risk for certain types of cancers. But I mean. So eventually, almost all of the I would say, for 80,

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* Kresge 502 Cart: almost all, all the people over a have certain kinds of these mutations. Whether or not it is frank cancer. It's debatable

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* Kresge 502 Cart: on the type of how you define cancer. Yeah, that's a great point.

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* Kresge 502 Cart: really great. But any other thoughts on that.

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* Kresge 502 Cart: Okay.

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* Kresge 502 Cart: okay. So I'm gonna go. And just to just to give you kind of a kind of so we can get some common terminology down. And again. So Dr. Weinberg and Hannah wrote this wonderful article in cell. Talking about some of the key fee hallmarks of cancer.

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* Kresge 502 Cart: So what is a tumor versus what is cancer? So tumor is really sort of a non dis nonspecific description of any sort of lump or spelling of tissue and a tumor can be both benign or cancerous. And so if you compare these 4 features the tumor invasiveness, the rate of growth.

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* Kresge 502 Cart: whether the cells look like the original cell of origin. So, for example, if it's a prostate cell, does it still look like prostate? Or does it look

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* Kresge 502 Cart: like poorly differentiated or d differentiates. It doesn't look like that anymore. Kind of metastasize. And then, if you compare benign tumors and malignant tumors, malignant tumors. I think the one feature that all tumors that are cancer have is that they're invasive and benign tumors are often sort of encapsulated in themselves, and they're not invasive into the adjacent tissue.

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* Kresge 502 Cart: This is not all. But the rest of the other features are not always true. Again, talking about prostate cancer. Prostate cancer that is invasive can actually grow very, very slowly some. Not all do. And similarly, breast. Maybe thyroid cancer in some cases can grow very, very slowly so, but more often than not malignant tumors will grow rapidly versus benign tumors, which have very slow, or even are not really growing at all.

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* Kresge 502 Cart: So again, in terms of the differenti differentiation, how much does it look like the tissue of origin? Malignant humans are often poorly differentiated, or even d differentiated versus well differentiated. And this is again, this is just looking under the microscope. The pathologist looks at the tissue and says, Does this look like the original tissue of origin or not, and then from metastasis, which means that the cancer leaves

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* Kresge 502 Cart: it's a regional organ and goes to a different part of the body. And I'll I'll talk about that in a moment. So it does. Malignant tumors don't always metastasize, but they often or can metastasize, whereas benign tumor will never metastasize. So can you think of an example, though. So you can see, these features of malignant tumors or cancer are are really much more aggressive, they often can cause death.

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* Kresge 502 Cart: Can a benign tumor ever cause death? Can you think of an example? If it does?

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* Kresge 502 Cart: Yes.

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* Kresge 502 Cart: so again, there's there's a number of hallmark features of of cancer. Essentially, it's it's doing a lot of different biologic pathways to allow it to keep growing to avoid signals that are telling it to either stop growing or undergrow cell death it needs as it grows it needs its own blood supply called angiogenesis to both

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* Kresge 502 Cart: get additional nutrients, but also take away waste and also some of the hallmarks of cancer involve being more invasive. And then ultimately, if you have a cancer growing in the breast tissue that then can metastasize it has to be able to set up in a different environment and be able to grow and proliferate as well.

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* Kresge 502 Cart: So again, these II don't think these are things that you not need to memorize, but I just wanna kind of show you. Kind of one is the growth between the normal tissue into invasive cancer. And then some terminology that talks about specific classifications of of of cancer. So first, we have 3 different

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* Kresge 502 Cart: descriptors of sort of either normal tissue or pre malignant tissue. So hyperplasia is just simply refer to the fact that you have an increasing growth of the number of normal cells in a tissue. But the normal. The cells look pretty normal. Otherwise they're growing. So you get growth. So you have hyperplasia. But these are unlikely to form cancer. They don't show any evidence

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* Kresge 502 Cart: of the stat disease, I think one, and again sorry to use so many examples of the prostate, but one of the conditions that affects a lot of older people with with prostate is a benign, prostatic hyperplasia and which is a benign enlargement of the prostate.

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* Kresge 502 Cart: The next one, though, is dysplasia. So in contrast to hyperplasia, you can start to see

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* Kresge 502 Cart: pre malignant changes of these tissues and the specifically of of epithelial cells, and if you look under the microscope, they're not invading right? They don't have the the features that the cancer has there. There. They might even still be slow growing, but they're starting to look atypical, and there's many cancers for which you have dysplasia as an evidence. And again, in some ways the hope for the early detection is not only that you detect

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* Kresge 502 Cart: cancer earlier, but that there are these pre malignant conditions, and the goal would be to actually identify those before cancer occurs, because then you could sort of remove them, treat them before the cancer progresses, and then carcinoma inside 2 are malignant cells that have all the features, otherwise of cancer, except for the invasiveness components. So that's carcinoma inside. 2

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* Kresge 502 Cart: and so just in terms of you know, once cancer occurs yes.

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* first of all, and said to

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* Kresge 502 Cart: in in insight, I think inside you right in. It's the it's sort of like

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* Kresge 502 Cart: so like I think breast cancer in side 2 is probably breast carcinoma in side 2. It's it's sort of like

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* Kresge 502 Cart: it's located still in the breast tissue. It just hasn't invaded into the adjacent organ. So inside to

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* Kresge 502 Cart: not activated

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* Kresge 502 Cart: activated just hasn't like just hasn't invaded into any adjacent organ. So it's probably still encapsulated to some extent.

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* Kresge 502 Cart: Oh, sorry. Yeah. Oh, I'm just wondering. Lower stage, it's not considered cancer. And we actually, there's some debate about this. We've actually, we've had some really interesting discussion. Love to hear your perspective on this. But you know, is it truly cancer? If it doesn't have that invasive

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* Kresge 502 Cart: feature? So I do. You have a thought about? If it's cancer type of cancer. So cervical cancer? Yes, no. Inside of means that there is a buzzer. Learn that cancer. So did not

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* Kresge 502 Cart: go across it and and and and invade it beyond that. That's what those good. That's the system about that. So

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* Kresge 502 Cart: the implication is different and and service, and and every type of sensor. So. as as you said, these are different type of diseases, so I can't really refer to. All of them is one. But

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* Kresge 502 Cart: inside, to usually means less in place. That's how I didn't didn't spread.

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* Kresge 502 Cart: Yeah, but it. But it's still it hasn't. Actually, you know, I think, that the distinction, if you, if you believe that you have to have these features to call it cancer like, even with Cervix, the insight to it still has not invaded into the adjacent tissue. So that but it's still the risk that it will is high, right? So it's really concerning you still wanna remove it? Is it cancer? Per se?

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* Kresge 502 Cart: It's important to like,

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* Kresge 502 Cart: II think this is correct. Cancer inside to

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* Kresge 502 Cart: is like

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* Kresge 502 Cart: what would happen had breast cancer.

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* Kresge 502 Cart: 2 of all those people

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* Kresge 502 Cart: there, there would be a risk. Answer. And relatively well, I mean, it's not

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* Kresge 502 Cart: over many years.

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* Kresge 502 Cart: 5%.

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* Kresge 502 Cart: And like for for color record.

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* Kresge 502 Cart: there is a actually indistinguishable from what we would call

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* Kresge 502 Cart: added, Oh, my, that's a precursor with high displacement. So if you, if you look just at the cells.

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* Kresge 502 Cart: looks pretty bad with some cancer, but it hasn't faded yet.

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* Kresge 502 Cart: But if you leave those regions again.

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* Kresge 502 Cart: like maybe into 5,

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* Kresge 502 Cart: you're great, slightly.

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* Kresge 502 Cart: Chad, or 20%.

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* Kresge 502 Cart: Yeah? Well, depending on the type of poly, right? There's different risk of cancer occurring, depending on the type of poly

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* Kresge 502 Cart: right? Right? Right?

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* Kresge 502 Cart: And actually, so, and trained actually as a pathologist before studying epidemiology. Just to few years. Yeah.

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* Kresge 502 Cart: so again, just to give you a lay of the land in terms of some of the like. Once cancer is occurring, the way that it gets described is based on where the tissue originated from. So

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* Kresge 502 Cart: sarcoma is a malignant tumor that is, arises from mesenchymal tissues, and it's usually defined by the tissue of origin, so a malignant tumor arising in bone would be referred to as an Osircoma carcinoma is malignant tissue that occurs in epithelial organs, and it's defined by

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* Kresge 502 Cart: the type of origin of the epithelial tissue. So again, for static carcinoma, and particularly if if it's occurring in these glandular structures, this is a lot of detail. But again, you're gonna hear these words. I just want to give you a sense of where they come from. When they are occurring specifically in the glandular structures of the epithelial tissue that's referred to as add no carcinoma. But instead of it's on the superficial epithelial cells.

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* Kresge 502 Cart: it's going to sell a personoma malignant tumors occurring in lymph nodes is lymphoma or from circling blood cells or bone marrows leukemia, and then finally, malignant tumors that derive from melanos sites is melanoma, so just can get the origin.

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* Kresge 502 Cart: And so this is really been interesting to think about how we might integrate. And all of this is is histology. So it's it's things that the pathologists is looking at under the microscope. And

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* Kresge 502 Cart: describing. So here's an example of lung cancer histology. So the vast majority of lung cancer is carcinoma meaning it's originating from epithelial tissues. But then you can break down the carcinoma into those that are small cell

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* Kresge 502 Cart: and versus non small cell lung cancer. And then within that non small cell lung cancer, you have 3 different bins 40 or so are abnormal carcinoma. 30 are squamous cell. And again, that just refers to the actual

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* Kresge 502 Cart: part of the epithelial tissue that's rising from, and then more rare, these large cell lung cancers. And so this is a figure looking at the association between the number of cigarettes smoked per day. And the relative risk of lung cancer that's in red is this squamous cell cancer? Green is small cell lung cancer and blue is, add no carcinoma. So when you look at this figure.

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* Kresge 502 Cart: what what does this figure

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* Kresge 502 Cart: say to you

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* Kresge 502 Cart: in terms of anything you could talk about? The overall association of of smoking and lung cancer. You could talk about the relative risk in terms of the different subtypes of cancer or not. No differences. What? What does this sound. Tell you.

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* Kresge 502 Cart: when you look at this cigarettes, quote per day. And the rest of

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* Kresge 502 Cart: all types of

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* Kresge 502 Cart: yeah, yeah, absolutely. And you can see it's pretty dramatic right? So compared to people are not smoking. You have a range of about 8 to probably 20 fold increased risk in those people who are smoking 30 or more cigarettes.

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* Kresge 502 Cart: and so does it look like. There might be a difference in terms of the strength of the association

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* Kresge 502 Cart: when we don't have confidence intervals here, so we can't make a statistical comparison. But if you were qualitatively saying, there might be a difference.

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* Kresge 502 Cart: Do you think there is

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* Kresge 502 Cart: maybe a little bit. Yes. Yeah. Yeah.

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* Kresge 502 Cart: Yeah, yeah, definitely. It looks like the strongest association are for cancers that are squamous cell cancers still significantly associate with. Add no carcinoma, but does seem to be not as strong of an association. And so the question is, why right is, you know, what is is it about the carcinogens. Is it based on how tobacco is taken up into the lungs? I think people talk about

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* Kresge 502 Cart: some of those things in general, but I think this is just an illustrative example that the association of risk factors and cancers, we're starting to realize may differ based on things like the histology of of the tumor, and we'll talk about some examples. I think, colorectal cancer. It also may be not only histology of meaning how it looks under the microscope, but also molecular features in the different cancer types.

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* Kresge 502 Cart: Yes.

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* Kresge 502 Cart: I. So

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* Kresge 502 Cart: oh, between small and non-smell. So so there, I think it's basically just the cell of origin. I'm not a lung cancer expert. So I think, but it's basically do.

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* Kresge 502 Cart: It was just a

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* Kresge 502 Cart: the historical one.

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* Kresge 502 Cart: I think it's based on installments.

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* Kresge 502 Cart: small cells. And so

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* Kresge 502 Cart: so

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* Kresge 502 Cart: balancing.

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* Kresge 502 Cart: it's it's

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* Kresge 502 Cart: relate to the type of mutations that are in the sales and also how they present small cell present

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* Kresge 502 Cart: within the central area of the one field, whereas and also we don't really operate how we treat them. So we don't really operate. Small cell

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* Kresge 502 Cart: can serve, whereas in.

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* Kresge 502 Cart: especially when it's not

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* Kresge 502 Cart: the.

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* Kresge 502 Cart: And do you do not do surgery in those because of the or where it's located in the lung

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* Kresge 502 Cart: cause it doesn't help interesting. Yeah, interesting. Yeah. Yeah. So it's interesting to think about all of the things that we like. We're thinking from the cancer epidemiology, lens of risk factors being associated with these different cell types. But they also have impact on prognosis, on treatment decisions, etc. So it's interesting to kind of think about how to integrate these into depending on what you're setting. So

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* Kresge 502 Cart: so metastasis is thought to be really the highest degree of malignancy and most cancer deaths occur because they've left the original

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* Kresge 502 Cart: tissue and have gone to another part of the body and cures really much less likely possible. At this stage. And interestingly, specific cancers seem to metastasize to different parts of the body. So, for example. Again, prostate is primary side of metastasis to the bone, and you can see here other sites, common sites of metastasis.

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* Kresge 502 Cart: So it is interesting to think about that. You know, you have cancer cells, let's say in the testis, in the bladder, in the kidney. They then have to get out of that or

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* Kresge 502 Cart: organ, and get either potentially through the blood systems. They may metastasize one that is, through nerves. One thought is through lymph nodes to other parts of the body, and then they have to be able to survive and then grow in that in that side of metastasis

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* Kresge 502 Cart: and then tumor grade. We talked a little bit about histology. So epithologists makes the diagnosis of cancer by looking under the microscope. And then also we'll try to give a sense of what's called the tumor grade. And there's 2 different main descriptions of grade. One is is called histologic grade, which is what the pattern of differentiation looks like, and you can sort of see

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* Kresge 502 Cart: this is things that are well differentiated, meaning they look more like the tissue of origin, and then, as they get less and less looking like the original tissue of origin, th they're they're thought to be more aggressive terms of prognosis. You may treat these differently, but also from an epidemiology perspective. You may be interested in studying, say, the association between smoking and a cancer

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* Kresge 502 Cart: that's either poorly differentiated. We've all differentiated. Come to the point that we talked about earlier, which is that you may not be interested in setting the risk of cancer overall, but rather the risk of cancers that are going to do harm.

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* Kresge 502 Cart: And then the other grading system that's used in some types of cancers is a based solely on the the shape and size of the nucleus, and that's called a nuclear grade.

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* Kresge 502 Cart: Again, this is again, just to give you kind of a background in cancer itself. And then so the other one of the other factors clinically, that's used. But again, we can think about this from our epidemiology studies is the staging of cancer, and for many different cancers. We use a system called T and M to define is the cancer still localized

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* Kresge 502 Cart: to the original tissue of origin, whether brass, prostate bladder, or has it? Gone beyond the origin? And so you look at sort of the extent of the tumors. It here, you can say, was, it's not detectable other than by screening, or can get larger, and then it can even go to the the borders, are there? Lymph nodes that are involved?

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* Kresge 502 Cart: and that can give you a sense of how aggressive the cancer heads. It's likely for spread. And then finally, metastasis to more distant organs. And you would usually use some sort of the imaging to assess whether the cancer is metastasized or not.

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* Kresge 502 Cart: And then, as I mentioned, for some cancers, we're learning a lot about the molecular subtypes of these cancers. Here's an example with breast cancer. So if a person is diagnosed with breast cancer, they'll get additional kind of

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* Kresge 502 Cart: biomarker workup to see whether they their tumors expressing the estrogen receptor progesterone receptor. If it's positive for her 2 or if it's triple negative. And again, that could be important for how the

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* Kresge 502 Cart: the physician will treat the cancer the likelihood of a bad or better prognosis, but also from an epidemiologic perspective. We're really starting to see with breast cancer and heather lies, and we'll talk about this in some detail that not all risk factors are the same for cancers that have the estrogen receptor present in the tumors versus those are absent. So she'll talk about that. And then we have some lectures on prostate and and colorectal cancer as well. Talking about some of the molecular subtypes.

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* Kresge 502 Cart: Okay? So just again, just to kind of wrap up this very biologic kind of discussion. When we think about how risk factors. Or, first of all, how cancer occurs. And as well as how risk factors may lead to either the prevention of cancer or an increased risk. We can kind of think about this, you know central dogma of going from DNA to Rna

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* Kresge 502 Cart: to protein, and then even to metabolites. And we, you know, Dr. Weinbergen is his

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* Kresge 502 Cart: In the video we played. And also, when you think about cancer, often think about these mutations in the DNA occurring, but not all cancers are occurring through simply through mutations. There can be effects that are not through mutations that are on the Rna level quantity, so how much the gene is turned on or off and then, or it could be to the translation going from Rna

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* Kresge 502 Cart: to protein is the protein expressed in high levels, has it been altered in some way? And so all of these things we can think about cancer the other way in which we can think about an infect on the DNA is actually not through a mutation, but actually through epigenetics. So some risk factors may be acting, not by doing damage to DNA, but actually by impacting

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* Kresge 502 Cart: something called epigenetics, which doesn't change the the DNA,

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* Kresge 502 Cart: you know letters but actually can modify. The way DNA works through a different modifications. So one important thing, just to kind of know, there's a couple of different ways in which genes and our DNA can be altered. The first is that they could be. You could get an altered copy from from your parents, so it can be inherited through the germline.

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* Kresge 502 Cart: You can also get sort of a

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* Kresge 502 Cart: alterations that can lead to what we call somatic damage or changes to to DNA after somebody's born. So, for example, I think lung cancer and smoking. You can think about that. You have sort of normal DNA that you've inherited that can then be damaged somatically. Through the accumulation of exposure to tobacco smoke. So that's a that's a key distinction, though.

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* Kresge 502 Cart: The DNA you get that's inherited that you get from the parents. And then DNA that can be damaged somatically. And that's after you know the initial

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* Kresge 502 Cart: you know your initial formation. This is, I think, a really interesting example of the impact on the environment on DNA, that's not through mutation. So this was a case study of 2 identical twins. So they were monozygotic or identical twins. Who are astronauts that were part of the Us. NASA Space program.

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* Kresge 502 Cart: One of the twins spent a year in space, while the other twin, who was also an astronaut, was on the ground. And they did some detailed biologics on these 2 identical twins and said, Well, do you know the DNA inherited DNA of these 2 individuals was identical?

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* Kresge 502 Cart: Right? Because they're they're monozygotic twins, or their inherited DNA was identical. But after spending a year in space

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* Kresge 502 Cart: they looked at the epigenetics and the impact of the environment on modifications to the DNA and found pretty big differences in the Gene expression of 800 genes that seem to be due to epigenetic modifications. They also showed shortening of the telomeres now, after some time of the. And I

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* Kresge 502 Cart: think Oh, no, I don't remember actually sorry. I'm not gonna say if I had to guess I don't know why I would think this twin was the one who went to space.

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* Kresge 502 Cart: It looks like right a little bit of an effect on aging in a little way, but I could be. No, I'm serious. No, no, it's true. I think this effect of biologic aging, right of the environment and epigenetics. So sorry. But I think I think this was the 21 space. But a lot of that. Actually, those changes in gene expression. kind of some of them went away. Some of them didn't. Some of them kind of stayed

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* Kresge 502 Cart: for a long time after. But you know, I think that epigenetics is something that is

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* Kresge 502 Cart: kind of potentially modifiable, whereas, like a DNA mutation is, unless you can get rid of that mutation through program cell death, or something like that is not modifiable.

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* Kresge 502 Cart: so so just kind of thinking about inherited genetic variation. When we look at the DNA of everybody in this room, 99.6% of our inherited genome is the same across all of us here.

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* Kresge 502 Cart: and so about one in 400 base pairs and the Mo. The majority of this variation is actually single nucleotide polymorphism. So it's a single alteration in a base pair. Lot of those things don't affect

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* Kresge 502 Cart: Rna don't affect protein. Some do. Some of the individual genes are different, and they do contribute, but some of them don't. And then about 10% of the genet genetic variations in the more structural. But a lot of the studies that we've done and trying to understand the genetics susceptibility to cancer have been focused on measuring these single nucleotide polymorphism. So again, about one in 400 base pairs vary

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* Kresge 502 Cart: between all of us, and whether some of those are associated with cancer or not. Associated with cardiovascular disease or other types of diseases is something we can do.

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* Kresge 502 Cart: You know, I'll talk about in a moment. So, as I mentioned already, these these sips may exist, but we don't know what they do. But then you might say, these sips are more common in this disease than in people who don't have that disease. And the question is, why, what are they affecting? Are they changing? Yes.

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* Kresge 502 Cart: yeah, yeah, that's super interesting.

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* Kresge 502 Cart: Thank you.

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* Kresge 502 Cart: so yeah, so

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* Kresge 502 Cart: so anyway. So so we'll we'll we'll talk about this when we start going into some of the discussion have. There's a great course, I think, on genetic epidemiology. If people are interested in getting more depth on some of the underlying genetic causes of disease. So if you're interested in this, but within some of the individual lectures, we'll talk about the role of inherited genetic factors

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* who?

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* Kresge 502 Cart: So I think I wanted to just kind of highlight these sort of 3 main classes of mutations.

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* Kresge 502 Cart: one is oncogenes tumor suppressor genes and DNA repair genes. And I think I think there's a great chapter that's in from the textbook of cancer epidemiology called the Origins of cancer. So people again, who won't want to read more up on the biology of cancer. It could. Guys goes into a lot more detail about this. But oncogenes are, you can kind of think of our the gas

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* Kresge 502 Cart: of of cancer. So kind of when when these genes are mutated, it's like the gas keeps the gas pedals down and tells kit grow, grow, grow, grow, grow, grow, grow, grow.

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* Kresge 502 Cart: tumor, tumor repressors. On the other hand, normally their role is to tell cells not to grow without a gross stimuli being present. And so what happens there when you get a mutation in these tumor suppressors? Basically, the great, the break is broken and so you stepping on the break. But nothing's happening. And so basically, you're

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* Kresge 502 Cart: the the cells are not no longer getting these signals to stop growing, so they keep growing, and then DNA repair. Jeans are those genes that are involved in sort of, you know, as as Dr. Weinberg said, you know you have

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* Kresge 502 Cart: millions upon billions of cell

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* Kresge 502 Cart: cell division happening. And by chance you can get mutations occurring. And so you need mechanism in place, and there's genes that are involved in the repair of of or cells, and either repairing the DNA damage that's occurred, or or telling the cell to undergo cell death. And so what can happen, though, is you can have mutations in these DNA repair genes. So they're not as effective in identifying

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* Kresge 502 Cart: when mutations are occurring and then getting rid of the cells. So these are kind of the 3 main classes. When we think about mutations in DNA, these are the kind of 3 main classes of of the types of genes that are involved in cancer.

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* Kresge 502 Cart: And so I think this is the last idea. And so there, there's a theory about this to hit hypothesis in in cancer. That it takes.

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* Kresge 502 Cart: you know, 2 alterations

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* Kresge 502 Cart: in the chromos like. So you have. You know you have 2 chromosomes so you need to have a mutation in both in order for cancer to occur. Now, if you have it. We'll talk about some inherited cancer syndromes at our next lecture.

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* Kresge 502 Cart: You can have from your parents. Unfortunately, one of your chromosomes has that alteration already, so it could be in an oncogene. It could be in tumor, suppressor, gene, or it could be in a DNA repair gene. So, for example, with breast cancer, you might get an inherited mutated copy of Brca. One, for example, or Brca. 2. That on its own isn't sufficient to cause cancer.

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* Kresge 502 Cart: but it increases the risk of cancer of happening so much because you already have the one strike against you. So you just need that second strike to occur in order for cancer to occur. So again, this PIN on the left kind of shows you you have. Your parental genes. One of them has a mutated copy. Unfortunately, you got that copy. So then you just need that second hit, that second mutagenic hit in order for cancer to occur

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* Kresge 502 Cart: in this example here, with the 2 hit hypothesis you happen to have from your parental genes no mutation there. You really have to get end up getting 2 mutagenic hits in the same cell in order for cancer to occur. So that's the 2 hit hypothesis. So again, this is just sort of an overview of some of the key concepts in

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* Kresge 502 Cart: kind of the path of biology, of cancer. At the next lecture we're gonna go into more about genetic susceptibility to cancer we're gonna talk about. Then also some of the more methodology talking about bias confounding. There's actually an article that would be great. If you can read before the class. Talking about recall bias. In case, control studies of cancer epidemiology.

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* Kresge 502 Cart: going to have a breakout discussion about that next time. So, any any questions, any thoughts?

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* Kresge 502 Cart: okay. Great. Well, excellent. We're really excited to have you all here feel free to email, any of us make sure if if anybody is having any trouble accessing the Harvard canvas page, email, any of us. And we otherwise we'll see you on Thursday.

1:26:57

* Kresge 502 Cart: Great thanks.

2.

* Kresge 502 Cart: Alright, so people are already starting to respond. So as we talked about on Tuesday, we always have a trivia question at the start of class. So this particular question talks about which of the following is not true. So one of these 4 answers is not true about

0:15

* Kresge 502 Cart: breast cancer. You can either join by the web you can join by text, or there's also a QR. Code. I don't know how close you have to be to scan it or not. But you have 3 different ways to answer. So the question is, which of the following is not true. Is it a. That the first mastectomy for breast cancer treatment was 1,500 years ago. B. That obesity be before puberty is associated with an increased risk of breast cancer.

0:39

* Kresge 502 Cart: Breast cancer has a higher occurrence in the left than the right breast, or that breast cancer can occur in cats and dogs. And it looks like we have 15 people who have responded for people just coming in. We'll give you about maybe 25 s to think about it.

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* Kresge 502 Cart: You can talk with your colleagues

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* Kresge 502 Cart: this is, can be a collaboration.

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* Kresge 502 Cart: 3

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* Kresge 502 Cart: of most people who wanted to give it maybe 10 more seconds.

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* Kresge 502 Cart: 5 more seconds. If anybody wants more time. Just raise your hand. We're going to call it.

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* Kresge 502 Cart: and and you just hit escape

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* Kresge 502 Cart: to see the answers alright. And the winner is

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* Kresge 502 Cart: response, history over here. Yeah, got it? Oh, interesting. Okay. So so many people thought that this was not correct, that breast cancer has a higher, higher occurrence in the left than the right breast. For some reason that's actually true. So about 51% of tumors arise in the left breast versus the right breast. According to my reading of the literature, there's no real explanation of why that is. But that

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* Kresge 502 Cart: is not true right? So that is an actual, true statement. So the actual, true answer is B.

3:02

* Kresge 502 Cart: So what you'll learn about breast cancer when Dr. Eliason gives the lecture is that excess body weight early in life?

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* Kresge 502 Cart: Well, that is.

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* Kresge 502 Cart: that's true. That is true.

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* Kresge 502 Cart: This is a typo. Oh, darn! Oh, I'm so sorry, so sorry. Oh, goodness, Ok, Major, fail.

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* Kresge 502 Cart: Sorry about that, guys. So, okay, so these are all actually, true answers. So, okay, that's that's too bad. But you did. But really interesting thought it was like a extra trick. Luckily it's it's doesn't count towards the grade. Okay, so sorry about that. I think. I remember that now from last year that it was a typo, and I think I carried it forward. So I apologize.

3:44

* Kresge 502 Cart: So first we wanted to talk a little bit about upcoming assignments. So your first assignment is going to be due next Thursday. So a week from today is that correct? Is that next Thursday, Tuesday. So we actually a week and a half. And it will be due by the end of the day, and it's

4:09

* Kresge 502 Cart: most helpful for all of us if you upload. Your assignment onto the Harvard canvas page. And so again, you're gonna be thinking in the mindset as if you're a reviewer for a journal. So you wanna think about reviewing the epidemiologic aspects of the study. So as I mentioned earlier, it's it's gonna be a study using the all of Us research program

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* Kresge 502 Cart: to look at the association between air quality and cancer risk. And there's a detail word document on Harvard canvas that goes through. How do you approach

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* Kresge 502 Cart: reviewing a a paper for a journal article? Usually you wanna look through and think about the study design? Are there potential sources of bias. Is the hypothesis sound? Have they taken, undertaken the study with with rigor? And so that the results? And and have they interpreted the results

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* Kresge 502 Cart: like correctly, or have they? Sometimes you'll see authors will overstate results. So there's a really detailed set of criteria in how to write up the critique, and it shouldn't be really long to be no more than 3 pages double space. And so our wonderful teaching fellows are gonna have an office hour on February first

5:31

* Kresge 502 Cart: from 3, 30 to 4, 30 in Cresc. 205. I wonder do you think it's possible to record it or have a zoom option? Would that be possible? And then for people who might not be able to attend, but might wanna hear with the discussion, so we'll post that onto the Harvard canvas page. So if you, if any questions come up, take a look at the Harvard canvas page about the structure and and way to think about this

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* Kresge 502 Cart: really want to kind of go through with the mind of an epidemiologist in thinking through the critique. And then. kind of later in February. The the one of the bigger assignments is the cancer epidemiology pro projects. And remember, there's 2 parts to this. There's gonna be an individual. Write up on the descriptive epidemiology of that cancer. And then, you, you're gonna have a group presentation where you present, not only on the descriptive epidemiology of cancer, but also on the association between a risk factor and cancer.

6:18

* Kresge 502 Cart: So starting at 50'clock today, so start thinking about which of these cancer sites you'd like to take part in. And do people sign up for more than one?

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* Kresge 502 Cart: Okay? And what happens if we have too many people, there's a cap. There is a cap. Okay? So if you're really excited about a certain cancer definitely, try to log on as soon as you can at 50'clock. So you can get in on that cancer. Honestly, each of the cancers that is listed here is really fascinating from an epidemiology perspective, both in terms of the descriptive epidemi epidemiology which really is like the patterns of disease

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* Kresge 502 Cart: in different populations across time, across different groups as well as risk factors. So I think there's a lot of interest in

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* Kresge 502 Cart: in these. so we'll talk a little bit more in detail about what each of the components looks like. But just to let you know that 50'clock today go to Harvard canvas and sign up self. Select for one of the cancers any questions on either of the assignments. Yes.

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* Kresge 502 Cart: Per group. Yeah, is it 5 or

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* Kresge 502 Cart: exactly. Yeah. Great. Any other questions.

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* Kresge 502 Cart: Okay, fantastic.

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* Kresge 502 Cart: Okay, so we're gonna delve into a little bit more into some of the the core methods and cancer epidemology and on Tuesday we talked a little bit about the role that family history plays in cancer. Which is interesting both in terms of thinking of it as

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* Kresge 502 Cart: a risk factor and try to understand the ideology of cancer. But also, things like family history can be used. You know, for example, clinically and risk prediction models. And looking at you know, which groups of people might need to have more regular surveillance, more regular screening, for example. So how do we? How, when you think about family history.

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* Kresge 502 Cart: of in doing an epidemiology study. How might you collect information on family history?

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* Kresge 502 Cart: What are some thoughts on where you might get that kind of information if you were doing an epidemiology, study

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* Kresge 502 Cart: questionnaire. Yeah? Yeah. So you could send out a questionnaire to. Let's say you have a case control study or cohort and just ask people, and how, what kind of questions would you want to ask? Do you think about if you were putting it on the questionnaire?

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* Kresge 502 Cart: Sorry I want to put you on the spot. But yeah, any thoughts about how you might ask some questions. 498, sex. Maybe specifically about family history. How might you ask the question?

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* Kresge 502 Cart: Answer.

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* Kresge 502 Cart: yeah, no. That's great. Yeah, really. Yes, in terms of shared exposures within the family kind of, yeah, yeah, absolutely. So, if you wanted to go into more detail about. You know what might be non genetic factors in family history. You might want to collect that.

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* Kresge 502 Cart: But right? So in the in the questionnaire. Right? You might. If you just wanna collect family history, you might wanna ask not only did has anybody in your family had breast cancer, prostate cancer, pancreatic cancer, etc. You wanna might wanna know what age they were, what relationship they were to you, and maybe probably with cancer. And if you think about genetic relatedness.

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* Kresge 502 Cart: you probably aren't as interested in, maybe say, cousins, etc. So you really might be thinking about primary like first degree relatives, whether it's your parents, whether it's your siblings, maybe even your kids. And then you might also wanna know if they died. And then, you know, with with the advent of of genetic testing, or even things like 23 me, it might be interesting to know, did you have any of that

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* Kresge 502 Cart: testing done, and could we get those results back? So if you were, let's say you had a cohort of

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* Kresge 502 Cart: you know, 10,000 people, ages 30 to 45 at the start of the study. What might be one limitation if you just asked at at the baseline about family history, can you think about about. Maybe I'm not asking the question exactly right. But so you have a group of people sort of early

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* Kresge 502 Cart: in midlife.

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* Kresge 502 Cart: and you're asking them about their family history. Yeah, I feel like some of their family might not be old enough to have undisturbed cancer. Exactly

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* Kresge 502 Cart: right? So you might not capture what really is family history? Just because maybe your siblings haven't gotten old enough. Even your parents might at that point might not be old enough to really be at the highest incidence of cancer. Exactly. Any other limitations you can think about of questionnaire-based information on family history

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* Kresge 502 Cart: if you wanted to.

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* Kresge 502 Cart: Yes, maybe to have a call one.

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* Kresge 502 Cart: Yeah. But observing, like you're not, there could be mistakes

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* Kresge 502 Cart: right? And so like. So there's 2 kind of interesting things with that. So maybe with a cohort study. Maybe just you can't remember right, you know. I think I think my dad had something. But don't remember, I don't. I don't remember. If they did, they really have prostate, or it was pancreatic cancer, right? So in a cohort study would be non differential right? So they would be as likely to over and underreport it. And so, yeah.

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* Kresge 502 Cart: yeah, exactly right. So underestimate the genetic risk, because people are dying from other things it would be interesting to think about is also, are there shared genes between those 2 causes of or the other way which would be interesting. And then, in terms of the recall bias.

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* Kresge 502 Cart: go back to your point. If it's a case control study. And so you're asking people who have cancer who don't have cancer. The people who have cancer may remember things differently. I often talk about it as rumination. Really. Why did I get this cancer? And

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* Kresge 502 Cart: you may think about it differently. Sorry about that right? Exactly. And so was there something somebody else said.

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* Kresge 502 Cart: So there's that. And then the other thing is, there may be people who don't know their family's history right? They may be they were adopted. Maybe there was a family member like a parent who was never part of that person's life. And so in certain populations, understanding family history is much, more, much more challenging. Well, there was not necessarily to get around this, but really interesting opportunity

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* Kresge 502 Cart: for investigating family history is in Scandinavia, where they're able to track

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* Kresge 502 Cart: cancer, hospitalization, death in the entire population. These things are required by law to be registered into these national databases, and they were able to create something called the multigenerational Register. This one particular. This data is from Sweden. So basically, they were able to go from the time the cancer registry first started in Sweden, which was in the 1950 s.

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* Kresge 502 Cart: And then track multiple generations so they could link the birth registers. So they knew who was related to whom in the register, and then they were able to tag on the how those people, whether the people had cancer or not. And then look at multigenerational family history. So I just wanna I think this is an interesting study design and interesting example. So this particular study included 2.2 million

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* Kresge 502 Cart: of women who are leading living in Sweden, in whom 54 0 cases of breast cancer occurred, and then these are the relative risk

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* Kresge 502 Cart: breast cancer in these women. If they had a sister only who had breast cancer, a mother, only 2 sisters, a mother and a sister and or a mother, and a brother, and all of those the reference group is no family history of cancer.

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* Kresge 502 Cart: So what? When you're looking at the relative risk estimates and 95% confidence intervals for risk of breast cancer with family history. What is this data

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* Kresge 502 Cart: kind of say to you?

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* Kresge 502 Cart: Right? So it looks like the the, you know. There's a stronger association. If you have 2 sisters, a mother, sister, and even a stronger with mother and brother. So why do you think that might be why do you think it might be that it's a little bit stronger with having more family members.

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* Kresge 502 Cart: What might that be saying about family history as an exposure?

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* Kresge 502 Cart: Yeah, it could be more may indicate when you have more family members that have the cancer, it might be more indicative that family history isn't just that shared environment that we talked about, but also, maybe more due to genetic factors. Exactly.

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* Kresge 502 Cart: So so one of the challenges with you know, family based studies looking at family history is exactly what we were just talking about, which is, is a family history of genetic factors, or is it not genetic factors? And one interesting epidemiologic approach? That people have taken is, instead of studying family members to really, specifically look at twins.

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* Kresge 502 Cart: What do you think is interesting? We I know we had. We talked about the twin astronauts. Being simple. So what do you think might be interesting about studying twins and the different types of twin pairs that might be able to kind of disentangle the effect of genes from environment in cancer. If you look at family history

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* Kresge 502 Cart: when you think about the types of twins there are. Bless you.

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* Kresge 502 Cart: genetics. Yeah, exactly. So. So if you you think there's 2 main types of twins, others, these on identical or monozygotic twins who share in theory 100% of their inherited genome. And then you have 50% on average share genetic factors in the fraternal twins or the dizygotic twins

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* Kresge 502 Cart: twins. And so you can basically like, you can look at what's your risk of breast cancer, for example, if your twin also had breast cancer, and then you can ask the question, how does that differ? If you're an identical twin versus if you're a fraternal twin, and then you can almost take away the environmental component by subtracting out the effect that you see in the dizzy twins and any excess

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* Kresge 502 Cart: concordance that you see in the monozygotic twins.

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* Kresge 502 Cart: then, you say is is likely due to inherited genetic factors. So this this was I was part of a project. I did my postdoc in in Sweden, and I was part of a really cool study of twins in the Nordic country, where they were able. If anybody's looking for interesting research projects, I think doing work in Sweden's came in. It was really fascinating.

19:01

* Kresge 502 Cart: They were able to in the 1950 s. Basically, they wanted to build this twin cohort so they were able to go back and get the records. These were handwritten records from each of the individual parishes throughout Scandinavia and identify when a twin birth

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* Kresge 502 Cart: was recorded, and at the time they didn't have genetics, so they would go then to the family and say, Do the did the twins look identical or or not, and to try to get at this fraternal versus identical twins. And then they built this registry of of over 200,000 twin pairs from the Scandinavian countries, and then again, because they can link it

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* Kresge 502 Cart: with cancer registries and mortality registries. They can follow up these cohorts for decades and see who develops cancer. And so this is a plot of the age looking at age of diagnosis on the X axis, and then cumulative risk of cancer on the Y axis. And then the gray line represents what's just the cumulative incidence of cancer in that population. And you can see it's about 33%.

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* Kresge 502 Cart: So it's kind of like the lifetime. Risk one in 3.

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* Kresge 502 Cart: And then, if your twin also had some sort of cancer and your dysa got a twin, the likelihood that you also would

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* Kresge 502 Cart: develop cancer during your lifetime is closer to 40%. And then, if you're an identical twin and your twin pair developed some form of cancer. Your own risk, was closer to about 46%. So sort of again, you can sort of see, there seems to be both a genetic and shared environment component that leads to the overall risk of cancer.

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* Kresge 502 Cart: So then you can one of the the concepts they use in in twin studies by sort of parsing out the effects of dizygotic versus monozygotic twins is called heritability, which is a simple measure, which is what's the proportion of the variability in cancer incidence that you can attribute to inherited genetic factors, and so overall about

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* Kresge 502 Cart: about 35% of the heritability of any cancer is due to inherited genetic factors. And then you can see this range. You have some cancers like colorectal cancer. We'll talk about colorectal cancer a lot about. We know a lot about modifiable lifestyle factors. And so genetic factors have a small role, but much more so environmental and lifestyle factors play a role

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* Kresge 502 Cart: and colorectal cancer. In contrast, prostate cancer. And then melanoma seem to have these very strong genetic factors. It doesn't mean it's only genes. It could be genes interacting with the environment, but they both have a strong genetic predisposition.

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* Kresge 502 Cart: So then, the question is, if anybody has any questions about any of these, just feel free to raise your hand. So then the question is, yes, the risk of cancer increases when the genetics and environmental

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* Kresge 502 Cart: well, I think Melanova is an interesting example, because it also, you know, some aspects of melanoma are due to exposure to UV radiation. And so the question is, maybe there's an underlying genetic susceptibility to which people are going to be more or less susceptible to UV radiation. So that's that's an example. One example of this idea where genes and environment

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* Kresge 502 Cart: interact together. Another example is in bladder cancer, where there's

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* Kresge 502 Cart: certain genes that modify. Your ability to metabolize alcohol. And so depending, 2 people can drink the same amount of alcohol, but you get differences in how that gets metabolized, and then that then leads to an effect on cancer. So it's together the genes and the environment together. So that's an example of gene environment interaction.

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* Kresge 502 Cart: So

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* Kresge 502 Cart: so when we think about genetic factors, and we talked about this a little bit. So remember, about 99.6% of the inherited genome is similar across everybody in the room.

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* Kresge 502 Cart: And and so the the variability that exists is actually quite small. The majority of that variability in genes are these

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* Kresge 502 Cart: things that are more common. Single nucleotide polymorphism changes just a single variant change in the DNA and these common variants.

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* Kresge 502 Cart: What we mean by common is usually that the prevalence in some population is probably 5% or more so, maybe not in every population, but in some populations about 5% or more. So these are very common, relatively common variation in the population. The flip side, though, is that most of them have very, very small effects on

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* Kresge 502 Cart: diseases. So when we look at cancer and we'll talk about a genome, wide association study. These individual genetic variants that are seem to be associated with cancer across multiple studies. Sometimes their odds, ratios, or relative risk estimates are very, very small

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* Kresge 502 Cart: at the other extreme. You have very, very rare

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* Kresge 502 Cart: variants that cause disease in a Mendelian fashion, meaning, if you have the gene. Unfortunately, you're gonna get the disease. So Huntington's is a prime example of that, that. If you have the very rare, it's a very, that very, very high likelihood that you're gonna if not completely likelihood, that you're gonna get the disease I can't think of.

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* Kresge 502 Cart: Maybe in cancer.

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* Kresge 502 Cart: If there's that sort of Mendelian, maybe some of the cancer syndromes get close, but they're much more in this middle phase. I don't know Ed or anybody. If you can think of an example of a true Mendelian trait for a genetic variant in cancer.

25:36

* Kresge 502 Cart: There's some that still like, I think we think a lot about Brca. One and Brca. 2 mutations in the germ line being strongly associated with the risk of breast cancer, ovarian cancer. But they're not fatalistic. So not everybody gets them. So

25:55

* probably a fake

26:14

* Kresge 502 Cart: he was for? Yeah. So it gets close to a Mendelian trait.

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* Kresge 502 Cart: Yeah. So so yeah, but you can kinda get this sense. There's this gradient and and the more rare the variants are the stronger the effect size is, and then more common variance tend to have very modest to low effect sizes.

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* Kresge 502 Cart: I already talked about this. So about 5 to 10% of

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* Kresge 502 Cart: cancers that have an inherited cause are due to these family syndromes or these more.

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* Kresge 502 Cart: we look at it, these lower frequency variants, or even

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* Kresge 502 Cart: the very rare variants causing Mendelian related traits.

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* Kresge 502 Cart: But for these families that have these

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* Kresge 502 Cart: germline mutations, they're pretty awful. The risk of certain cancers occurring is very, very high, and it gets passed from generation to generation. And we'll talk about a couple of these hereditary cancer syndromes specifically

27:22

* Kresge 502 Cart: and what they look like in the types of cancers that they have. But there's there can be many cases in a family with the same type of cancer, especially if it's uncommon or a rare type of cancer. And we looked at, we talked about that with the family history in the Swedish generational cohort, that when you saw 2 sisters, or you had a mother and sister, or mother and father a brother, your risk was was

27:43

* Kresge 502 Cart: matiring is probably more likely these were due to a hereditary cancer. Other features of hereditary cancer syndromes are cancers occurring in the sex not usually affected. I think breast cancer is an example of that. And if it's occurring in multiple generations.

28:07

* Kresge 502 Cart: so these are probably some of the most common of these hereditary cancer syndromes. I'm going to be talking about Leif Ramini, and a little bit about lynch syndrome, and I think when Dr. Song comes in lectures he'll talk more about lynch syndrome and its role in colorectal cancer and other cancers as well. And then I'm going to talk a little bit about Lee Rermini.

28:27

* Kresge 502 Cart: Dr. Lee was a faculty member here at the Harvard School of Public Health, together with Dr. Fermini, who was at the National Cancer Institute. We'll talk about as well. And then, of course. Brca, one and Brca 2, and breast cancer and ovarian cancer are probably pretty well known to you. Interestingly, they seem to be playing a role in other cancers as well. So again, these are the more

28:52

* Kresge 502 Cart: lower prevalence, more moderate moderate effects. So they're they're playing a role in the development of male breast cancer prostate cancer, probably pancreatic cancer as well.

29:16

* Kresge 502 Cart: So leaf Ramini, how do I get rid of this? Sorry? Yeah. Got it? Thank you.

29:28

* Kresge 502 Cart: So the lifer-mini syndrome was really identified by Doctors Lien formini back in 1,969. And they were really interested in the Gene, p. 53 which plays a broad role in cell growth in cell cycle arrest in DNA repair-related mechanisms.

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* Kresge 502 Cart: It can play a role in apoptosis which is basically programmed cell death, and it can eliminate any damage cells. So it plays a really important role in cellular growth as well as making sure it gets rid of any bad.

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* Kresge 502 Cart: This cell division, just as Dr. Weinberg was kind of talking about. It helps scan and make sure that any of these cell divisions are not resulting in mutations.

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* Kresge 502 Cart: So however, in cancer, when you look, remember the difference between germline and somatic when you look somatically at tumors. So if you looked at the Germline, DNA. Take a blood specimen and look at the DNA that's going to really reflect the DNA that came from the parents.

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* Kresge 502 Cart: You might not see at all probably won't, for in the most case, unless there's this family syndrome in the tumors, however, it can be quite common, and it's probably one of the most commonly mutated genes in in tumors across an array of cancers. So it's realized that when you basically have these mutations, all of a sudden, all these great repair DNA repair pathways, apoptosis, etc. Go away.

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* Kresge 502 Cart: But what lean from Media, I realized, was actually there are people in which their germ line has a mutation already, and so, if you remember the 2 hypothesis

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* Kresge 502 Cart: carcinogenesis. So if you, if you get one bad allele

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* Kresge 502 Cart: with a p. 53 mutation. All you need is one more in order for cancer to be occurring. So so you're already kind of

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* Kresge 502 Cart: more than halfway there in getting cancer. So how they identified this was, they studied families, and there was really an interesting array of cancers ranging from high prevalence of osteosarcoma, melanoma, brain breast cancer, leukemia, few others in these populations. Very early on set before the ages of 45,

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* Kresge 502 Cart: and the risk of cancer in the populations was quite high, and they were able to show that this was due to p. 53 mutations that were inherited. So germline mutations were in this family.

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* Kresge 502 Cart: and so unfortunately, while you can't probably prevention, for these families may be hard. These aren't populations that you'd wanna do much more intensive surveillance at much younger ages. So a very interesting kind of tidbit about in cancer was identified, probably, I think, about 7 or 8 years ago. When somebody asked the question, why do elephants have such a low

32:26

* Kresge 502 Cart: mortality from cancer. So with other animals, the larger the size, and the older they live, the greater the mortality from cancer. And so, if you compare the mortality from cancer in humans to that of elephants, you can see the lifetime mortality from cancers between, say, 10 and 25% in elephants in 4.8

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* Kresge 502 Cart: in terms of average lifespan. It's pretty similar body weight much much higher. So there's more cells. So just by chance, you think you might develop more cancer in elephants? So you can see, this number of cells is is exponentially higher. What was determined, though when they did sequencing of the elephant was that while humans have 2 copies, right? We have 2 copies, alleles of elephants actually have 40.

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* Kresge 502 Cart: So that's pretty interesting. So they all are slightly have slight modifications in the proteins they produce, but there's so much redundancy in this pathway, so, instead of having to knock out 2 alleles in elephant, you'd have to knock out 40, actually, as a tidbit.

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* Kresge 502 Cart: I learned that mammoths. They also mammoths which are now extinct. They're able to get DNA from mammoths also show they have a very high copy of p. 53 alleles in their

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* Kresge 502 Cart: in their DNA oops.

34:23

* Kresge 502 Cart: Okay, so lynch syndrome. And then feel free to just hop in on this. And I know, as I said, Dr. Song is gonna have a lot more detail. So lynch syndrome occurs when there's inherited mutations in a type of DNA repair called mismatch repair genes. So these are specific genes that are involved in a type of DNA repair, called mismatch, repair. And this leads to a syndrome

34:28

* Kresge 502 Cart: hereditary non polyposis, colorectal cancer and as as you were saying, egg what you can see here is that while the risk of colon cancer in the general population is about, say, 5 in a family with lynch syndrome, the risk of colorectal cancer is about 80. It's also quite elevated. The lifetime risk for indonesal cancer about 60% compared to about 2%

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* Kresge 502 Cart: in the population. Also, elevated risks of stomach, ovarian cancer, and some other cancers as well.

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* Kresge 502 Cart: Anything else sad?

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* Kresge 502 Cart: Yeah, we'll be talking more about it. So in terms of the discovery. So all of those family syndromes are really again, these more moderate effect, size, genetic mutations, but whose prevalence is pretty low. So again, at a population level.

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* account for so much of the genetic susceptibility to cancer. So a lot of what we know now about what causes cancer in terms of inherited genetics has come from doing genome-wide association studies. And so this is where you take.

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* Kresge 502 Cart: Now, we understand, we really need to have sort of tens of thousands or hundreds of thousands of cases of cancer, you know, tens to 100,000 controls. And then look kind of it's really a discovery effort. You're looking at millions of individual, single, nucleotide polymorphisms and sort of saying, are any of these

36:12

* Kresge 502 Cart: much more common in cancer cases, or even less common in cancer cases? And the way we look at that is in something called the Manhattan plot. And the idea is, it looks like, you know, a cityscape. So basically, you're plotting on the X axis is what chromosome the Snps are on, and then on. Y-axis, you take the negative log, 10

36:32

* Kresge 502 Cart: p. Value. And so, and then, because you're looking at millions of single nucleotide polymorphisms. Usually you set your P value fairly, conservatively at 10 to the minus 8 here. And so any of those variants that are above that P value threshold are, you would say, are associated with the cancer you don't know

36:57

* Kresge 502 Cart: is the prevalence higher or lower, because it's just a P. Value. But these are the variants that seem to be kind of potentially interesting. But also this isn't meant to be a course on genetic epidemiology. But the question then becomes like, are these the variants that are causing the cancer to occur? Or are they just really close by to another genetic variant that maybe isn't tagged as well in the array, etc. So there's additional work you'd want

37:21

* Kresge 502 Cart: to do here. Now I can say so. This is actually a Manhattan plot from prostate cancer. And so all of these variants that are popping up here are variants that in multi-ethnic and in multiple populations are significantly and reproducibly associated with the risk of prostate cancer.

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* Kresge 502 Cart: The individual effect of these variants, though, is really small. So the relative risk, if you looked, if you have this variant versus. If you don't, the relative risk might be 1.1 1.2. So really, really small.

38:04

* Kresge 502 Cart: But now, as of a couple of weeks ago, or maybe a few weeks ago, the latest publication, we've identified over 450 of these individual genetic variants. So then, the question is, well, maybe if one variant so you're not getting much of an effect. What if you took all of the variants together and created some sort of score? And that's what we do with apologetic risk score. So you're basically

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* Kresge 502 Cart: looking at each of these 450 barons. And you're basically like, right, here's

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* variant one. Do you have it? Yes or no.

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* Kresge 502 Cart: plus variant 2,

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* Kresge 502 Cart: yes or no, and maybe you weight it by the strength of the

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* Kresge 502 Cart: you take your betas from the odds, ratios, and maybe so, if area one had an odds, ratio of 1.3 and variant 2 had an odds ratio of 1.1. This one's gonna get weighted a little bit stronger. And then you add those up. So now what you can see, though then in this Polygenic risk score. You can look at people who have the highest genetic risk, because maybe they have. You know, 100 of the 400 variants versus those people who have the lowest genetic risk. Maybe they have

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* Kresge 502 Cart: 0. Maybe they have 5 of those risk variants. And you can really start to see big differences in risk prediction. And so this, I guess, is just to say, now,

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* Kresge 502 Cart: you know, in terms of the these Gwoss studies have really helped to. Maybe maybe not so much. We can't think about prevention per se. But you can really start to think, could you use this like for early detection of cancer, for example. So if you knew somebody had they were in the top. This is the top one percentile of the polygenic risk, for so they probably have the most variance. Their lifetime risk of prostate cancer is 65.

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* Kresge 502 Cart: If you're in the bottom tenth percentile of the genetic risk, your lifetime, risk of of prostate cancer is closer to to 2.

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* Kresge 502 Cart: So you can really start to see this ability to risk stratify over a person's lifetime. All right. So we'll take it. Yes. understand how.

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* Kresge 502 Cart: So I'm trying to connect it to the previous slide the man has. Are they related somehow? They are

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* Kresge 502 Cart: this, I mean. This is an older version of of the Manhattan plot, but in this was an older. Anyway, it doesn't matter. Let's just say there are on this plot, 450 unique genetic variants, with a P. Value greater than 10 to the minus eighth.

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* Kresge 502 Cart: that are associated with prostate cancer. And then you make a simple score, and you take each variant.

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* Kresge 502 Cart: and for each person say, Do you have it or not? Yes or no? If you don't have it.

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* Kresge 502 Cart: then that doesn't go contribute to the score if you have this one, and then let's say you don't have any of the others. Your total score is gonna be based solely on this one variant. But some people have 50 variants or 100 variants. And so, depending on how many variants you have, you can create these polygenic risk scores. And then, basically, all you're doing is dividing it into 10 equal groups.

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* Kresge 502 Cart: It's a very simple quartiles or quantiles. For instance, if someone has less variance. Then there's going to be lower, right. If they have less variance, their score is going to be lower and their lifetime risk in this case of prostate cancer is gonna be much, much lower. So you might not see as strong of an a curve like this is basically looking at the absolute risk of cancer over someone's lifetime. Your risk

41:39

* Kresge 502 Cart: of of colorectal cancer with a polygenic score. It's probably gonna look pretty, not gonna look as impressive. Remember, prostate and melanoma were the 2 cancers in the twin studies as well as in family based studies that have the strongest inherited genetic component. Now we've identified a lot of genetic variants. And you can really start with these polygenic risk scores to be able to say something about future risk.

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* Kresge 502 Cart: Do we use them, and do they copy? Not yet.

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* Kresge 502 Cart: But people are doing that to say, could you use this as part of an early detection strategy? That's the question for cancer.

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* Kresge 502 Cart: but we aren't using them clinically. Now.

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* Kresge 502 Cart: now this that remember, this is snps. Now that's different than say for lynch syndrome.

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* Kresge 502 Cart: where, if you are a family member and who's part of a family that's known to have Lynn syndrome? Then you are, Gonna use that genetic information. You're gonna go to a genetic counselor hopefully at a affiliated with a cancer center. And you're gonna be followed closely. And for a range of of potentially different cancers. So that's it is being used clinically in these kind of cancer syndromes.

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* Kresge 502 Cart: There's other examples, too, but the Ji-wa snips, I would say in general, I haven't been translated yet. Any other questions.

43:26

* Kresge 502 Cart: Okay? So the next 2 slides are really getting at

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* Kresge 502 Cart: basic descriptive measures of cancer.

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* Kresge 502 Cart: Yep, so we have an incidence rate a mortality rate and a fatality rate. So pulling back from intro epie, what is an incidence rate? And how would you calculate it?

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* Kresge 502 Cart: What are the 3 components that would go into calculating an incidence rate

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* Kresge 502 Cart: number of new cases in

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* Kresge 502 Cart: yep, right? And then the third piece of it. So you have. So the interest rate.

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* Kresge 502 Cart: The numerator is the number of cases of cancer in the population in the population usually usually present it

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* Kresge 502 Cart: per 100,000 people. What's the other element. That's important time. Exactly. Right? So usually in a year, you might say, so, what's the annual incidence rate of cancer, or every 5 years, or something.

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* Kresge 502 Cart: Okay. So mortality and fatality, what's the difference?

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* Kresge 502 Cart: What's mortality rate? Yep. And again, with time? Exactly right? So it's very similar to incidents, because the it's the number of cancer deaths.

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* and then denominator instead, the number of cancers

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* Kresge 502 Cart: divided by the population and then

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* Kresge 502 Cart: over time.

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* Kresge 502 Cart: Here. Ca, so then, what's fatality? What's the difference. There? I'm talking about fatality. Which group of people am I looking at? Am I looking at the whole population? No, what am I looking at?

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* Kresge 502 Cart: Only the cancer cases. Exactly right? So fatality, then, and this is this gets

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* Kresge 502 Cart: confused all the time. In fact, there was this paper that was like a response, like a letter to the editor. Actually, that was written about this exact thing because there was a paper that kept talking about mortality rates. But actually, but they were actually talking about fatality rates. So fatality, the denominator are just people cases with cancer.

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* Kresge 502 Cart: And in the numerator there's the cancer deaths. And again, it's over time.

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* Kresge 502 Cart: So can you think of a situation where you might have a high fatality.

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* Kresge 502 Cart: but a low mortality?

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* Kresge 502 Cart: Can you think of a a cancer

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* Kresge 502 Cart: when the cancer has a very low incidence rate, but a high fatality. Exactly right? So cancers like pancreatic cancer liver cancer, they're kind of on the rare side. So in terms of

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* Kresge 502 Cart: the population level, the mortality rate looks much lower than for other cancers. But really, when you look at the vitality, so what happens in people who have the cancer, it can look pretty pretty awful. And it is so that's an example where the mortality is telling you something a little bit different. It's really a population level statistic versus the fatality which is really telling you, what's the prognosis in people who have cancer?

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* Kresge 502 Cart: Okay, so what's problems. Then

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* Kresge 502 Cart: what's the prevalence of cancer? If you were trying to?

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* Kresge 502 Cart: What statistic does that refer to

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* Kresge 502 Cart: existing cases at that time? Yeah, yeah, exactly. And so, what are the factors that go into prevalence

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* Kresge 502 Cart: like? Is there an example where you could have

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* Kresge 502 Cart: trying to think like a high incidence, but a low prevalence.

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* Kresge 502 Cart: Do you remember the formula for calculating prevalence?

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* Kresge 502 Cart: Yes, there's yes, exactly right. So if you have a highly fatal cancer, the prevalence may look kind of low because the duration someone's living with that cancer is is very short. So even if the incidence of size. So basically, this is a simplified formula, incidence, times duration.

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* Kresge 502 Cart: Looking at the

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* Kresge 502 Cart: I was gonna write that. And I was like, that's right, right. It's a simplified formula. Yeah. So if your incidence is high, but your duration is low, your prevalence is gonna end up being pretty low. And then have you ever heard of the concept of years of life lost?

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* Kresge 502 Cart: Yeah. And what is what if you could just like, sort of give a descriptor of what that is? Here's a life lost that's close. That's that's Dali's or disability adjusted life here. So here's a life loss literally is you know you not only count

48:49

* Kresge 502 Cart: that it's a death, but the age at which someone died. So it's sort of for for childhood cancers. These can rank very, very high because the amount of years of life lost can be quite significant. So that may be a figure. Oh, yes, yeah.

49:15

* Kresge 502 Cart: exactly so in the formula here they usually use 75. II don't know if they've changed it now, but they generally think like, if someone had lived a full life they would have lived to 75 years. How many years did they lose because they were a child, and they died at say age 8, or something like that for them they would have lost

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* Kresge 502 Cart: 67 years of life, and then, for cancers like prostate cancer, which the age at which people were dying might be 75, 80, even though the mortality might be high. Actually the years of life. Loss is not as much because you're dying around this time you would have died anyway.

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* Kresge 502 Cart: Yup, I think it was based on the on what the expect. Life expectancy was probably 2020, 30 years ago. So that's why I'm saying I don't know if they changed it, or if they always still use 75 but that was sort of, I think, based on the actuary tables in in within the setting of the United States, right? Because other countries have different age life expectancies.

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* Kresge 502 Cart: Alright. So here, this is data. And we're gonna in the descriptive epidemiology project, the group project that you're gonna work on. You're gonna get to work with. Some of these international cancer epidemiology, databases that will provide you with incidence mortality, prevalence across different populations. So. This is the crude

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* Kresge 502 Cart: incidence rate per 100,000 people of cancer in different countries, and the darker the blue, the higher the incidence rate, the lighter, the blue, the lower the incidence rate. So what might be a goal of looking at a map like this? What? What? Why might you want to

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* Kresge 502 Cart: make comparisons like this across countries.

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* Kresge 502 Cart: Or or maybe you could even just say, just looking at this map. What what does this tell you about this particular. I think this is total cancer incident. So what is the rate of cancer? Yeah, so it's it's, where is it? Maybe more concentrated? So this is just the crude rate per 100,000 people. Yup.

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* Kresge 502 Cart: it can help visualize disparities. Yeah, exactly right. So are there populations that seem like there are greater risk for this cancer.

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* Kresge 502 Cart: If I told you that the average life expectancy, let's say, in parts of Africa, might be 15 or 20 years lower than say in North America.

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* Kresge 502 Cart: and how might you? How like? What might you want to try to do to

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* Kresge 502 Cart: say, how much is there still a difference. We're independent of the fact that there's a different age of distribution.

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* Kresge 502 Cart: Yeah, age adjust. Exactly. So you'd wanna account for those age distrib. And you can see this really clearly here. This is looking at the age distribution in countries that are considered to be low and medium resource, countries versus those that are high resource. So you have in the lower and medium resource countries. You have much younger

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* Kresge 502 Cart: distribution of ages and more people in those age groups than you do in the high resource country. So if you wanna make these kind of comparisons, sometimes you wanna take away the effective age, and to do that, you can do age standardization. And it's just sort of a very simple concept, which is you basically would take the population into different age groupings.

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* Kresge 502 Cart: And you take the actual number of cancer deaths in those age groups, the actual number of people in those age groups and for a specific year. And that's how you would get the actual crude incidence rate per 100,000 people.

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* Kresge 502 Cart: That's generally how it's presented. And then you'd say, Well, I'm going to take the same

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* Kresge 502 Cart: distribution of ages and apply it to each country. So that the basic question, like, What would the if I assume that the rates of cancer. In these age groups are

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* Kresge 502 Cart: true rates. Then I apply a different distribution of age. So everybody has the same age distribution. What does that age adjusted rate look like. So does that make sense kind of what the distribution is doing. So basically, like.

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* Kresge 502 Cart: now, every country is going to have this same distribution of age in it. But I'm taking the actual rates of cancer in the individual countries for those ages. And then I'm getting an adjusted rate.

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* Kresge 502 Cart: Does that make sense.

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* Kresge 502 Cart: Alright. So we're gonna take a, we're gonna have a little breakout now. So this is a real example. So there was a group in upstate New York that wanted to look at

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* Kresge 502 Cart: prostate cancer mortality rates to see if there were racial disparities in in prostate cancer mortality. So they had the number of cancer specific deaths in white men and black men. They then had the number of men living at the time. Who were either white or black, and then per 100,000 people per year, and

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* Kresge 502 Cart: they calculated the prostate cancer mortality rate in white men to be 28.7, and in black men to be 28.9 per 100,000.

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* Kresge 502 Cart: So 2 pieces of data to think about one is that here's the distribution of age

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* Kresge 502 Cart: in white men.

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* Kresge 502 Cart: And here's the distribution of age in black men. So just to say that black men had generally a younger age overall in the population compared to white men.

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* Kresge 502 Cart: Right? So you can see that you have more older

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* Kresge 502 Cart: men who are white than in the black men. And the other fact is that mortality from prostate cancer increases really exponentially with age, so that the rates are about 100 times higher in men 65, and older compared to younger men.

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* Kresge 502 Cart: Alright. So the question is to have a quick discussion is, if you were to adjust the rates between black and white men. So they have the same age distribution. What do you think would happen? And what do you think you might see in terms of whether or not there might be differences in mortality between white and black men. So take just a minute or 2 and talk about how you think the mortality rates adjusted for age would look like between these 2 groups of individuals.

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* Kresge 502 Cart: logic of what you think

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* Kresge 502 Cart: could potentially happen. So so the question that we're trying to answer is.

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* Kresge 502 Cart: are there racial differences in prostate cancer mortality that are not due to age? Right? So that the question is really is that we don't want it to be about age differences, right? Because right now, on average, the black men in the whole population are younger than the white men. So we wanna say, is there a difference?

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* Kresge 502 Cart: A racial difference? We see that is separate from any difference that there might be from age. So what what were your thoughts qualitatively on, on what might happen if you did an age adjustment or age standardization?

1:00:07

* Kresge 502 Cart: I said, there's there's 3 potential answers. Right? 1 one answer is, there's no difference in the the crude estimates are gonna look similar to the A. The age adjusted estimates. One estimate is that the black men will look worse, and the other is that the white men will look worse. So so just show hands who, you know, discussions who thought they'd look the same.

1:00:22

* Kresge 502 Cart: and then who thought they would look? The white men would look like worse mortality.

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* Kresge 502 Cart: And then who thought the black men would look like they had worse mortality. So what was your logic behind that?

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* Kresge 502 Cart: Oh.

1:01:02

* Kresge 502 Cart: yes.

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* Kresge 502 Cart: just for

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* Kresge 502 Cart: exactly. And it's because there's such a strong association between age and prostate cancer mortality rates. So even if the mortality rate in each of the age groups was sort of similar, you're gonna upweight. What's happening in the black men. And you're gonna downweight. What's happening in the white men? So ultimately, you're gonna see that there are racial differences in mortality from prostate cancer from this population. Exactly.

1:01:16

* Kresge 502 Cart: Okay. Great. So now I'm gonna go into some of like the core epidemiology basics. And I'm gonna you know, I everyone has taken the intro to epidemiology core. So just as a reminder, there's kind of 2 core study designs we use. The the cohort study and the case control study. This is a hypothetical example of looking at the association between infection with HIV

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* Kresge 502 Cart: and the risk of Non Hodgson lymphoma. We will talk a little bit about this in the infections in in cancer lecture. So in this case, you'd start with a group of individuals where nobody had cancer at the start of follow up, so you wouldn't want anybody to have the cancer of interest at the start of follow up, and you'll know there, there'll be some people who are were exposed to HIV infection and

1:02:11

* who weren't. And then you can follow

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* Kresge 502 Cart: these groups forward and see which of them develop non-hodx and lymphoma, and which of them do not? So that would be sort of the cohort. Approach. And even, you know here I've just made it very simple that you're either exposed or unexposed at the start of the study. You then get a little fancier and say, I'm gonna keep asking about HIV infection over time and and people might become exposed later on.

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* Kresge 502 Cart: So we do case control studies where control studies are often done in cancer, particularly when cancers are rare

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* Kresge 502 Cart: right? Because even if you had a cohort of 100,000 individuals for some cancers like glioma, or maybe childhood cancers or cancers that are fairly rare. You're gonna have to have such a large cohort and follow people for sufficiently long enough to be able to have enough cancers cases in in your cohort. Just as an example

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* Kresge 502 Cart: we work with Ed and I and Michelle and colleen work with a cohort called the Health Professionals follow up study. It was started in the 1,986 50,000 people who identified as men at the start of the study. They've been followed now for over 36 years, and I think there are just over about 150 liver cancer cases.

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* Kresge 502 Cart: There's some bilary tract cancers, probably 40 or 50 that have occurred. So you can really see, even though we had this really large study and a really long follow up, there's still some cancers where the the incidence rate is so low in that population that's not really sufficient. So in that case, what you could do instead is identify your cases in some way. Think about

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* Kresge 502 Cart: what's the source population. That's not always easy, and we'll give a quick example of that in a minute. And sample people who don't have the cancer. And then assess the exposure. And one of the really important things is that you want the exposure frequency in the controls

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* Kresge 502 Cart: to represent the cohort

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* Kresge 502 Cart: that gave rise to the cases. You basically want the at baseline that controls should give you an estimate of the exposure distribution in the cohort that gave rise to the cases, and if you do a case control study well, it can be really an efficient way of an alternative to a cohort study. But there are a lot more issues of bias. And we'll talk about those kind of in a moment.

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* Kresge 502 Cart: And

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* Kresge 502 Cart: you know, just when we think about what what things do we measure in a cohort study versus a case control study? We often will measure. I think the big focus is really on relative measures. So what's the relative risk of cancer in the exposed group versus unexposed group? You might calculate an odds ratio. Maybe it's a hazard ratio. You can also think about absolute measures of a factor of risk differences.

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* Kresge 502 Cart: Another measure that you might see in epidemiology studies relate to either attributable fraction or population attributable fraction. So the difference there is with the attributable fraction. You're just saying of the cases.

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* Kresge 502 Cart: what number or what proportion of the cases of cancer can be attributed to the exposure, whereas in the population attributable fraction, the question is of

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* Kresge 502 Cart: in the whole population, what proportion of cancer can be explained by the exposure. So so they give you kind of slightly different measures. And so the idea is within the triple fraction. If you got rid of the exposure. Let's say it's smoking. Let's say it's an occupational exposure. If you could completely get rid of it

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* Kresge 502 Cart: in the cases, what proportion of the cases would be prevented versus in the entire population. You're taking the prevalence, not in the cases, but in the full population.

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* Kresge 502 Cart: Can you explain again the difference between the 2. Yeah, sure. So I think the big difference really is that the prevalence of

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* Kresge 502 Cart: well, let me talk about a trivial fraction first. So here we had 1,400 cases. Let's say we had. And you can see there's a population of 100,000 people.

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* Kresge 502 Cart: You have 1,400 cases in total, 900 of them didn't have the exposure in this situation. So the the attributable like none of the cases there can be attributed to the exposure. So you're just looking at the exposed cases. What per proportion of those

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* Kresge 502 Cart: can be attributed to the exposure? And this is really driven by the strength of the association of so something like lung cancer and smoking. You're going to have a much larger proportion of the cases, or is attributed to smoking than you would for something where maybe the relative risk estimate is much smaller. What's different here is in the population. Trivial fraction is

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* Kresge 502 Cart: that you're looking at a different prevalence of exposure. You're using the prevalence of exposure from the full population instead of from the population of cases.

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* Kresge 502 Cart: Am I kind of

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* Kresge 502 Cart: very simplistically, I'll look to my teaching fellows for that. Yeah.

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* Kresge 502 Cart: alright. So let's talk about confounding. This is a real example actually of a project that I was working on with a student looking at physical activity and lung cancer. And this was a cohort of 40,000 women. They had at study enrollment, collected detailed information about how much physical activity, what they were doing, what types of physical activity they were doing.

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* Kresge 502 Cart: and if, looking at the association between participating in the highest quintile of physical activity. The relative risk of lung cancer was

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* Kresge 502 Cart: 0 point 2 5 compared to women who have the lowest levels of activity. So basically saying, that you could lower your risk of of lung cancer by 75% by engaging the most physical activity. So if you looked at this. Can you think of a confounding factor that you might be worried about that? It's not physical activity. That's the risk factor, but that there's there's some additional factor that's correlated with physical activity.

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* Kresge 502 Cart: And on its own as a prospector for lung cancer. Okay? Bmi, that's interesting. Yep, smoking. Yeah. Any other awesome.

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* Kresge 502 Cart: Yeah. So I think smoking was probably the one that was the strongest cause. The the association between smoking and lung cancer is probably a relative risk of about 10 to 20. Remember from that figure over the lifetime. Yeah, Bmi is interesting, cause it's so strongly related to physical activity. And Bmi is an interesting one. And we do talk about this at all about like Bmi and lung cancer. And what happens like.

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* Kresge 502 Cart: you know, some people who have regressive forms of cancer might lose a little bit of weight before the cancer diagnosis because of the cancer is not detectable. But pancreatic cancer is a big example where you actually have weight loss before diagnosis. And then, of course, with smoking you might look like you have a lean body mass because of the smoking. So body mass is a really interesting one

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* Kresge 502 Cart: for this. So anyway. So by adjusting for smoking, actually, and what we did was first we adjusted for just ever smoking. So the relative risk went from being really really strongly protective to still looking pretty protective. But then, when you also adjust for the amount of cigarette smoked and the years someone smoked.

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* Kresge 502 Cart: Then essentially, what you can see is that the relative risk went almost to one meaning. There was no association between physical activity and lung cancer that the observed dissociation you had was completely due to confounded by smoking.

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* Kresge 502 Cart: Okay, so here's here's an example I want you to think about and remember what I talked about with case control studies. So this is a study that was led by 2 full professors at the time. And some other family members from the Harvard School of Public Health. It was actually one of them was my advisor, and he always used this as an example of what can go wrong in studies.

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* Kresge 502 Cart: So they published a study in the New England Journal of Medicine. It was a case control study looking at the association between coffee consumption and pancreatic cancer. It's a hospital-based case control study.

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* Kresge 502 Cart: and they recruited 369 cases of pancreatic cancer from 11 hospitals in Massachusetts and Rhode Island. And then they said, Remember it was a case control study. So they had to say.

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* Kresge 502 Cart: what was the source population that gave rise to these cases, meaning people who might have other diseases, who still would have gone to the hospitals had they developed the cancer. And so what they decided to do was to sample from the same 11 hospitals in gi clinics, from the same physicians where the pancreatic cancer patients were.

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* Kresge 502 Cart: and they had either other cancers or gi conditions. When they did this analysis they found that the relative risk of pancreatic cancer, if you drank one to 2 cups of coffee per day was 1.8, meaning an 80% higher risk compared to no drinking coffee, and if you drank 3 cups of coffee per day. It went as high as 2.7 cups per day, and they adjusted for cigarette smoking, which

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* Kresge 502 Cart: they thought could be an important confounder. So it used to be that people who drank a lot of coffee were more likely to be smokers, and smoking is a risk factor for pancreatic cancer. So they still found a positive association.

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* Kresge 502 Cart: So talk for a couple of minutes and think about given the design. Why do might they have seen this positive Association Association. Do you think it was causal adjusted for cigarette smoking they had just for other confounders, or what might it? What could have happened in the study design that led to this finding. So talk. This is a little bit more complicated, maybe talk for like 3 or 4 min, and then we'll come back together.

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* Kresge 502 Cart: Ok, so let's hear your thoughts on on some of the discussions you've had.

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* Kresge 502 Cart: So

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* Kresge 502 Cart: so what were some of the things you talked about in your groups.

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* Kresge 502 Cart: No, but it's actually really nice to call out each other and support each other, too.

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* Kresge 502 Cart: like defining the expansion of copy not being shared with

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* Kresge 502 Cart: clocking conceptions that

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* I think I said

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* Kresge 502 Cart: I just so could be. It could be a couple of things. It could be sort of recall bias in a way that, remember, comes to the other points or the pancreatic cancer is really ruminating about their causes. So they're gonna recall things differently. But then the other thing you mentioned, and so go into that a little bit more when you said you don't know if it's

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* Kresge 502 Cart: the exposure before or after the diagnosis. So what was your thought there in saying that specifically. or did somebody else want it? I don't want to put you on the spot.

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* Kresge 502 Cart: Did somebody else want to kind of follow up on that.

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* Kresge 502 Cart: Do you think having pancreatic cancer could impact how much coffee somebody's consuming potentially? Maybe you're feeling sick. Or maybe you're you're having some gi symptoms. And so if you're if you sort of yes.

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* Kresge 502 Cart: yes, yeah. So these are both great points. So in the cases you really want to think about what? What is the window of time? That somebody might be reporting on their coffee consumption. So so remember the odds ratio essentially. The way you're calculating is what's the odds of exposure in the of the exposure, in the cases

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* Kresge 502 Cart: divided by the odds of exposure and control. That's sort of one way to think about the odds ratio.

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* Kresge 502 Cart: right? So you could have recall bias right? That is, these people are ruminating, and they're overreporting. How much coffee they had compared to. And let's say, there was.

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* Kresge 502 Cart: There was no issue here so that could inflate the odds ratios potentially. So the point about the what's interesting about in this scenario, but great thinking about how a case controls so they can infect the exposure. So it's probably less likely that you know. Let's say they even let's say you even asked like how much coffee you've been drinking the last year. Maybe they had been drinking less because they were feeling ill

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* Kresge 502 Cart: in this case for the cases that would actually then lower the odds. Ratio right? But the point that you just raised, which is a great one is.

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* Kresge 502 Cart: look at where they got the controls from. These are people with other Gi conditions. So they're the ones like you want the control to represent the exposure distribution in the population that gave rise to the cases. So this is too low, right?

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* Kresge 502 Cart: And so then, that can also inflate the odds ratio as well. And so they actually did a follow up study to this doing a more appropriate selection of the controls. So they weren't able to get deal with recall bias. But we'll talk about, recall, recall bias in a second, but they were able to then show that there was no association. Between coffee and pancreatic cancer when they more appropriately dealt with the controls in that way.

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* Kresge 502 Cart: Okay, so let's talk about recall Bios. So this was one of the papers we were hoping that you had a chance to read before class. And so

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* Kresge 502 Cart: who wants to give like a really quick synopsis of what? That

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* Kresge 502 Cart: study the design of that study, because it was a pretty cool study that Dr. Jovanucci did as a student. Were you a student then? Or you just graduated?

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* Kresge 502 Cart: Yeah, I think it was 1991. Was the publication. Yeah. So you might have like, yeah, graduated. And then it took a little while to publish it. Yeah, I think it was 91. Maybe it was a little later. So what was the really cool design that Dr. Jovanuji did

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* Kresge 502 Cart: so. I guess. What was the premise? What was the premise?

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* Kresge 502 Cart: Why did you do this study

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* Kresge 502 Cart: so? He wanted to kind of. So there was a hypothesis out there that consumption of dietary fat

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* Kresge 502 Cart: was associated with an increased risk of breast cancer, and most of the studies

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* Kresge 502 Cart: that had been done on this topic had had been done in case control studies. And so there was a concern of

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* Kresge 502 Cart: recall bias. Potentially. Again, this idea that people might be ruminating. So he did this really cool design, which was, he had access to a cohort of nurses

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* Kresge 502 Cart: called the nurses health Study. There was a food frequency questionnaire that was asked and collected all sorts of information about the types of food someone ate, and they were able to calculate different types of of dietary fats from these foods, and then they followed people forward

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* Kresge 502 Cart: for breast cancer. So this was the cohort analysis. This is going to be in theory 3 of recall bias.

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* Kresge 502 Cart: So they identified 398 breast cancer cases. They also did age-match controls from the population, and then in 1,989. They went back and said, Hey, 3 years ago, tell us about what you ate right. But they actually had what they had reported in 1,986 before any cancer had occurred. So then they could.

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* Kresge 502 Cart: He had both. The recall diet after cases were diagnosed, and the actual diet that was recorded before. So does that make sense kind of what he was able to do.

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* Kresge 502 Cart: And so what did you find? So this is looking at odds, ratios, and 95% confidence intervals. The first column is looking at the Association of Total Fat Consumption of breast cancer risk, and then the second one specifically saturated fats in the risk of breast cancer. The first line of data is prospective cohort analysis, and then the other. One is

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* Kresge 502 Cart: more of the case-controlled techno analysis. So what did they see in those 2 different approaches? And do you think this showed? Recall bias or not?

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* Kresge 502 Cart: Yeah. So what does it say to you in looking at the data? If you were writing it up in a paper, what would you

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* repeat the models of quality.

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* Kresge 502 Cart: Yeah. And it was specific to the cases because they were the ones really, they had the disease. So they were really thinking of it. And that's why you get this inflation? Because it was just in the cases there might be misremembering on both groups. But that would be non-differential. But here it was clearly a differential type of bias. Exactly. Yep.

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* Kresge 502 Cart: yeah, right? That's a great point. So these, this is a cohort of nurses who are working in healthcare. They may be more familiar even than a general population with the literature that, hey? There might be this connection between dietary, fat and breast cancer risk. So anything you wanna add, or

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* Kresge 502 Cart: hypothesis made of time? It's made of a graph

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* Kresge 502 Cart: case control. Did you say.

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* Kresge 502 Cart: Teresuba? I said that. Well, this probably only applies to the US.

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* Kresge 502 Cart: Okay, right? Right? So that's interesting. So it could be a concern of recall bias in one population. And, as you said, because they're nurses and more engaged in the healthcare system. Maybe it's more of an issue there, that's really interesting. Yeah.

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* Kresge 502 Cart: so I think just to kind of wrap up. We've talked a little bit about measurement error, which you know, it's usually a non differential type of bias. You have recall bias you could have selection bias which we talked a lot about with the pancreatic cancer example. We talked a little bit about this, but and I think we'll talk about this in depth with pancreatic cancer. But other cancers as well. There's this sort of preclinical

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* Kresge 502 Cart: phase where the cancer exists, but it hasn't been diagnosed as of yet in some cancer patients, when the cancer is more aggressive, can actually lead to weight loss. So there were some studies in a pancreatic cancer looking at body mass index and pancreatic cancer, suggesting that there was an inverse association. So that higher Bma was protective against

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* Kresge 502 Cart: pancreatic cancer. But it really was because of this reverse causation that it was the cancer leading to weight loss. Now, this is gonna be interesting because Brian Wolfen is gonna come talk pancreatic cancer, how they're taking reverse causation and turning it into an early detection opportunity, right? Because the weight loss, then, is a signal that you could use to detect pancreatic cancer earlier, some other things as well. So it's interesting to think of a bias actually being an advantage.

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* Kresge 502 Cart: and then we're gonna have a great lecture that Michelle and colleen are gonna lead talking about survival analyses and that's gonna be great and talk a little, maybe a little bit about this kind of bias as well. That'll be later. In the course. And then finally, I just wanted to raise in cancer. You know, we talk about confounding one of the strongest confounding factors can actually be screening

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* Kresge 502 Cart: right screening when you screen somebody for cancer. The risk is much much elevated right? You know. Psa, a prostate specific antigen for prostate cancer, colonoscopy for colorectal cancer. Is so strongly related to the outcome. And then we know there's sort of like this. Healthy, you know, kind of lifestyle

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* Kresge 502 Cart: affect that. People who eat a healthy diet and engage in physical activity and maybe don't smoke are probably the ones more likely to get cancer screening. So diagnostic biases. Really, I think of really a form of confounding due to screening habits. And so that's something that's gonna be highlighted across different lectures and something as you're reading the literature that you might wanna be thinking about. For example, in your

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* Kresge 502 Cart: critiques. You might want to think about it if it's an issue. So

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* Kresge 502 Cart: just to wrap up in the last.

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* Kresge 502 Cart: No, I'm not going to, because, given the time. I'll I'll bring these last few slides into our lecture on Tuesday. Talking about like latency. I think, will be great. So just to wrap up a reminder that the office hour is going to be on

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* Kresge 502 Cart: next next Thursday after class, and it will be recorded so if people can't make it. That is great. Remember, at 50'clock today

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* Kresge 502 Cart: the Harvard canvas is gonna open. So you can sign up. For which of the cancers you wanna work on and then finally, we're gonna put in the link. The journal of the National Cancer Institute, just came out recently with an announcement. They really wanna they wanna focus on early career investigators. And so we're gonna put a link in that talks about if you're interested in submitting to that journal

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* Kresge 502 Cart: articles, or if you want to get experience. Being a peer reviewer for the journal, which is a great thing to have on your Cv. You can sign up, so we'll be sending that link out anything else that we want to have a great weekend, and we'll see you on Tuesday.

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* Should I end the meeting for everybody. Yeah.

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* Kresge 502 Cart: exactly. So. So again, the trivial traction just refers to. Only among the cases a proportion of the cases could prevent. If you got rid of the exposure of just the prevalence of the exposure. And so I think the key difference with the population attributable

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* is, instead, you're using the prevalence of the exposure in the full population, which often can be lower. So, for example, if you were looking at, say, smoking and lung cancer.

3.

* Kresge 502 Cart: I think we'll get started. I think. First we have an announcement about the groups for the descriptive Ethi project.

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* Kresge 502 Cart: Yeah, I would say by Thursday. Also, it's great if you guys can start meeting with your groups and sort of just introducing yourselves and then I on the on the description on Harvard campus. You'll see which of the 4 of us that you'll wanna set up a meeting because the goal is, we just wanna make sure you're especially when you pick the risk factor that there's enough

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* Kresge 502 Cart: epidemiology literature on it and give you some structure about how to review the literature present put the presentation together, etc. So any questions about that assignment?

1:00

* Kresge 502 Cart: Okay, great. And then on Thursday we'll we'll make a announcement. A reminder about the tf, tf, session for the first assignment of people want to attend that as well as when it's due, etc. Okay, so as always, we are gonna start with a trivia question. I think it's correct this time. So which of the following is not true. So before the following is false about tomatoes and the antioxidant lycopene which is

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* Kresge 502 Cart: found in high buns and sweet tomato products, one for a. There's an annual potato fight in Spain, involving hundreds of thousands of tomatoes.

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* Kresge 502 Cart: B. There's more lycopene bioavail in raw tomatoes than those cooked in olive oil. C the concentration of lycopene in the prostate is much higher than other tissues in the body, and D

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* Kresge 502 Cart: quote Prego, your prostate's best friend, was a press release citing Dr. Jovanucci's Landmark study. Looking at the association of Tomatoes and prostate cancer risk. So which of these is not true?

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* I think.

2:24

* Hello!

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* Kresge 502 Cart: It's like people are still kind of logging on. Alright! There we go!

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* Kresge 502 Cart: I'll see if we can get it to 15, and then we'll slowly close down the pole. We're up to 12, 13,

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* Kresge 502 Cart: 13. We get 15. We're so close. 14. Alright, I'm gonna close it down. Oh, amazing! Alright! 5, 4, 3, 2, and one, right? So 2. How do you? How do you get 2

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* Kresge 502 Cart: right here? Yeah, perfect.

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* Kresge 502 Cart: Okay? So it looks like

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* Kresge 502 Cart: about 61% of people, or about 58% of people, said Bee, which is the correct answer. So actually, when you either, you know, if you're making tomato sauce and you're cooking in some sort of oil, or even making a salsa, you know, putting olive oil on top of it. That basically licapine is a lipophilic. And so you need that to make

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* Kresge 502 Cart: the the like being more bioavailable. So actually, for some interesting reason, we don't really know why. When people eat a lot of cooked tomato products lycopene concentrates in the process at very high levels.

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* Kresge 502 Cart: It's also very interesting when people are exposed to heavy metals, those heavy metals accumulate in the prostate. Some things like selenium accumulate at high levels. And I think my general sense is we did a deep dive and and talking to pathologists and basic scientists. Why is this? And nobody really had a good answer. But it is interesting that when you eat a lot of cooked tomato products, the lcapane constitutes in the prostate, and

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* Kresge 502 Cart: Dr. Jovanici, do you want to mention anything about your your study, your landmark study on tomatoes and prostate cancer?

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* Kresge 502 Cart: Well, I don't know, because Conrad Stopsack is giving the lecture this year.

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* Kresge 502 Cart: They and they, they may be affiliated with my family, but I'm I'm not sure. So we're not. We're not. There's no need for disclosure, I guess, in in. So yeah. So Ed led a really important study. II think showing in the health professionals follow up study that the the men who regularly consume tomato cooked tomato products had a much lower risk

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* Kresge 502 Cart: of prostate cancer, and particularly more aggressive forms of prostate cancer. And I think there's been some debt. But, as you see, with the lecture on Prostate cancer, there's a lot of issues epidemiologically and methodologically that you have to take into account. So I really believe the evidence is fairly

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* Kresge 502 Cart: convincing. About an inverse association. And then a there it started many, many decades ago. But there's a small town in Spain which, right after the tomato harvest, they it started as a food fight, and now every year. It's it's like an attraction where people come, and it's sort of sad to waste all these beautiful tomatoes, but they have a they have a.

6:07

* Kresge 502 Cart: and ultimately a fight and state. So okay.

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* Kresge 502 Cart: so I'm gonna start out first up for about 25 min, and then Ed is going to take over. And so first I wanted to kind of wrap up where we ended last week and sort of talk a little bit about this concept of time in cancer, epidemiology, studies. I think it's it's.

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* Kresge 502 Cart: you know. I actually ran into Joel Schwartz. And we were. We were talking about extreme temperature and mortality. And how many of those studies that have been done about like looking at very exposure to very high, although temperatures with mortality have looked at a really short window of exposure. But we know for many, many types of cancers. It actually can be years, if not decades.

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* Kresge 502 Cart: between when someone first has the exposure of interest, and ultimately, what when cancer occurs and that varies for the type of a cancer and also varies for the type of exposure that it is. I think there's also an interesting thought about the way the kind of 2 main classes of the way exposures work. There's sort of

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* Kresge 502 Cart: 2 types of exposures that we think about initiators and promoters. The initiators are

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* Kresge 502 Cart: those kind of factors that probably do damage to DNA. Initially, it's like that's first initial hit. But it's not that. It's not submission for cancer to occur. You need things along the way that are promoting, maybe through, maybe not by damaging DNA, but more through, for example, inflammation or sending

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* Kresge 502 Cart: creating an environment of growth factors or other things that are helping fuel, the growth and the development into something that eventually

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* Kresge 502 Cart: becomes cancer. And so depending on whether something's an initiator which maybe will happen years years before or promoter, which you might see associated or closer to the cancer development. That plays around to timecourse. So just a kind of a few different thoughts. You know one thing when Dr. Lysand. Lectures. What you'll see is that in in terms of the age, specific incidence

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* Kresge 502 Cart: of breast cancer.

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* Kresge 502 Cart: So this is age. And so here's menopause, which on average probably occurs early fiftys that initially, after.

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* Kresge 502 Cart: you know, probably around childbearing age, the incidence starts increasing really sharply and then around menopause, it still increases, but that rate of increase kind of slows down. And so, thinking about what factors might be playing a little in this part of the curve versus this part of the curve has been a lot of research. So, thinking about cancers that occur pre menopausally as well as post menopausally. And Dr. Elizabeth.

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* Kresge 502 Cart: we'll go into that in more detail. So I got this. I really got this wrong on the trivia quiz. But for breast cancer, and maybe even for prostate cancer. Actually, the level of adiposity that one has as a child or during adolescence, seems to be actually associated with a lower risk

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* Kresge 502 Cart: of premedibosal breast cancer. Also, as I mentioned, prostate cancer, where whereas it's associated with an increased risk of breast cancer for prostate. It's interesting when you think about age again and thinking about puberty.

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* Kresge 502 Cart: When when a child is born with a prostate, it's actually still about the size of a grain of rice, and it doesn't really start going through full growth until puberty and for breast tissue. What you'll see with Dr. Lyonsen's lecture is that from puberty into that window of child-bearing age. The

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* Kresge 502 Cart: of tissue doesn't really start until the first pregnancy. And so there's thinking about time. Course. So not only is obesity associated with cancer. But what is the timeframe in which it might have an effect is an important consideration in your studies. So when we're reading the literature or doing your own studies. You want to kind of take that into account in some way.

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* Kresge 502 Cart: Height is really an interesting exposure. Height is associated strongly with an increased risk of many, many different types of cancers. And again, if you think about when children really start to grow, it's around that time of puberty. So again thinking for prostate cancer or or other types of cancers like what else is happening with the organ of tissue around puberty being

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* acceptable window of exposures with height, you have growth, factors, etc., happening.

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* Kresge 502 Cart: And then the other kind of extreme. When we think about really short time courses, we think about some of the childhood cancers. Which you know so probably those are things that are occurring, maybe in utero, or maybe just after birth. And then you're seeing pediatric cancers forming within the first year or 2.

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* Kresge 502 Cart: This is an interesting Analysis in radiation and cancer, and tried to understand what is the susceptibility of different tissues to radiation. Depending on age. And this is specifically looking at a range of studies that looked at different types of exposure to radiation and risk of breast cancer. And so

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* Kresge 502 Cart: this dotted line is looking at some. This is called the excess relative risk. I don't know why, but in radiation, epidemiology studies, they often look at the excess relative risk. All that is is relative risk minus one. So it's just how much excess risk beyond one is there. So on. Y-axis is that, and then on the X axis is the age of exposure, and what you can see, and this is the lifespan study was is a follow up of

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* Kresge 502 Cart: people who were exposed to radiation during the bombing of Hiroshima and Nagasaki. So these are people who did not die as a result of the the bombings, but were exposed at different ages, and then have been followed prospectively over time, and I think what you can sort of see here is that the the kids who were exposed

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* Kresge 502 Cart: early in life had the most strong association with future breast cancer risk, say 40 or 50 or more years later, and with time that excess risk

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* Kresge 502 Cart: is still there, but has attenuated substantially so. If someone instead was exposed at age 40 or 50, while there still is a small excess. It's not as dramatic as it is earlier in life, meaning again that window of susceptibility. And then these were a number of other studies. For example, there was a study done

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* Kresge 502 Cart: on tuberculosis patients, and and so what would often happen with tuberculosis is you'd have a collapse of the lung. And then you'd use fluoroscopes to guide back inflation of the lungs and fluoroscopes were almost like real time movies of using radiation. And so women were getting very high doses

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* Kresge 502 Cart: of radiation if they had Tb and had undergone fluoroscopy. So again, these were women at these ages, so not quite as strong with excess risk. But certainly the bombing is long and sustained. Increased risk. Any questions about this

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* Kresge 502 Cart: so just in terms of the concept of latency, and this slide was adapted from Igwyn Zhang, who was a student and now is a post-doctoral fellow in cancer epidemiology. Looking at, really thinking about the time frame from when someone first has an exposure, radiation, smoking diet.

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* Kresge 502 Cart: when the initial initiation

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* Kresge 502 Cart: of carcinogenesis is when tumor starts to develop and proliferate. And then, when it's first clinically detectable, and that

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* Kresge 502 Cart: the measured latency this is kind of, I won't go to a lot of detail about this. But just to think about the measured latency period is when we first measured have information on when the exposure occurred. So you might ask, for example, when did you start smoking cigarettes, or when did you have? You know your first Tb, fluoroscopy, whatever it is, from the time that the cancer is then detected. And that's the the latency.

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* Kresge 502 Cart: That's a period of time between when the first initiation happens and when cancer occurs.

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* Kresge 502 Cart: and a really strong example of this is in smoking and lung cancer. So what you can see they almost mirror each other exactly on the green line, looks at the increase in cigarette consumption over time among men in the United States. And then, 20 years later, what followed was

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* Kresge 502 Cart: a strong and positive excess risk of lung cancer mortality for 100 people, and you can sort of see across

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* Kresge 502 Cart: each of these time points with increasing consumption. You have about 20 years or so difference before you see the effect. And so this is where we get this idea that there's about a 20 year lag between smoking initiation and lung cancer incidence.

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* Kresge 502 Cart: Another interesting example of this is this was actually a randomized

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* Kresge 502 Cart: well, it was, yeah. It was a randomized trial of low dose aspirin and cancer risk, and this was after long term, follow up of about 18 years. So this was where people were randomized to 100 milligrams of aspirin or placebo. There was an initial 8 years of follow up on treatment, and then an additional 8 years post trial follow up. So the the

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* Kresge 502 Cart: more solid line are the people who were randomized to aspirin, and the more daubed line are those who are on the placebo. What is this?

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* Kresge 502 Cart: Kids would tell you say to you about possible latency or not?

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* Kresge 502 Cart: So time. 0 is like the start time of enrollment into the tribal

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* possible. More cancer.

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* Kresge 502 Cart: Sorry? What's that? Yes, exactly right. So the incidence is higher at the end of 18 years of follow up of compared to aspen. So the asthma is associated with a lower incidence of cancer. But what about the latency?

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* Kresge 502 Cart: When do you start seeing a potential lower risk in the aspirin group? How long did it take?

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* Kresge 502 Cart: 10 years exactly and so again. So the trial, the first, the follow up initially, was 8 years, suggesting there was no benefit of asthma, so it wasn't until the 10 year mark when you start to see this departure, and it makes sense. And I think Ed will talk a lot in in studies of diet and cancer. Why, you might see differences between randomized trials which often follow patients.

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* Kresge 502 Cart: participants for a relatively short time versus observational studies that can follow people for decades, and this idea of latency in a lagged analysis.

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* Kresge 502 Cart: And then so how might we study this? Epidemiologically? Well, this is just an example of a study that Ed was ed-led, looking at full weight, consumption, and the risk of colorectal cancer. And how do association really differs by time? And so within 2 of the cohorts based here at the Harvard School of Public Health, the nurses, health study, health professionals follow up study. There's information on diet

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* Kresge 502 Cart: every 4 years, and so that allowed the researchers to estimate every 4 years total, fully intake from diet or from supplements.

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* Kresge 502 Cart: And then we could look at. So in order to try to understand

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* Kresge 502 Cart: the impact of when folate might be important in terms of risk of cancer, they undertake undertook a number of different analyses where they were able to lag the exposure and sort of say, instead of looking at

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* Kresge 502 Cart: right, your exposure here, do you have cancer? 2 or 4 years later. Okay, let now let's see what you were doing.

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* Kresge 502 Cart: 0 to 4 years ago, 4 to 8 years ago, 8 to 1212 to 16, and then look at that and see which window of exposure is more important in terms of risk of colorectal cancer. And what was interesting to see. And this is a pretty busy slide. But what just to kind of take home this message that the really the strongest

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* Kresge 502 Cart: association of Foli intake being associated with a lower risk of colorectal cancer, was in the 12 to 16 year lap. You really had to look at what somebody was doing 12 to 16 years beforehand to look at the risk of colorectal cancer.

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* Kresge 502 Cart: Alright. So I'm gonna jump ahead, any questions on kind of the latency.

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* Kresge 502 Cart: Okay?

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* Kresge 502 Cart: So so I think it's really interesting to study the

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* Kresge 502 Cart: more where it's kind of developing. Yeah, so yeah, so, latency is this concept of how much time between when the exposure first started.

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* Kresge 502 Cart: or when at least it was first measured.

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* Kresge 502 Cart: and the time when the cancer was actually

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* Kresge 502 Cart: diagnosed. So that's sort of that whole period of latency. So for Folate, you really needed to look back at what someone was doing 12 or 16 years before the diagnosis in order to see this inverse Association.

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* Kresge 502 Cart: So when it says 10 year latency, it's just that specific time at which they were able to diagnose it. You know, you mean for the aspirin study. Yeah. So the aspirin study was basically, they were just observing people what happened to them. And they basically didn't see any divergent of the curves until 10 years. So with an initial trial for this.

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* Kresge 502 Cart: they had followed people. If I were correct, 8 years.

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* Kresge 502 Cart: and they followed up and said, Then there's in this randomized trial. There's no benefit of aspirin of cancer risk.

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* Kresge 502 Cart: However, when they follow people longer, that's when they start to see this divergence. You're starting to see the time between that initial exposure

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* Kresge 502 Cart: and cancer risk

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* Kresge 502 Cart: of 10 years. Cause? That's when you start to see the benefit.

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* Kresge 502 Cart: Yeah, in the forward study. Does it only count for the initial sculpture. Does it account for the duration? Well, in a way, it does account for the duration of what happened

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* Kresge 502 Cart: before 12 just I. But I think the way this analysis was done was specifically kind of what was your exposure at 12 to 16 years. But you're kind of constantly updating that. And and so that because you have cancers that were diagnosed in 2,000, 12,020, but you're always sort of moving that information forward. So you can say, what am I doing in 1986? And I'm gonna look

22:44

* Kresge 502 Cart: forward to cancer incidents diagnosed in 1,998. Now, if I want to look at cancer, diagnose in 2,004, I'm going to move ahead and say, All right. Now, what are you doing in 1,994.

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* Kresge 502 Cart: So you're kind of moving. Yeah, you're taking into account all of that information. But you're lagging kind of when? What? That initiation of exposure is

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* Kresge 502 Cart: any other questions?

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* Kresge 502 Cart: Okay? So I think that descriptive epidemiology is really interesting. And Bert Hoffman had this great lecture back in the fall on descriptive epidemiology and its important role in identifying outbreaks of disease and thinking about novel exposures, etc. It also is important, of course, in terms of the burden of cancer and

23:37

* Kresge 502 Cart: identifying where cancer is occurring now and where it might be occurring in the future. So let's get to some numbers. So globally, over 19 million new cancer cases are diagnosed and we'll show in a moment. It's more common in men than in women and about 10 million cancer deaths occur each year. But there's considerable variability

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* Kresge 502 Cart: across the globe in the incidence in mortality rates from cancer.

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* Kresge 502 Cart: This is looking in. Again, globally, globally, cancer ranks. If you put all cancer deaths together, it ranks second, after Cbd, this was not updated, because I think if you looked now, I think COVID-19 deaths would would really probably rank

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* Kresge 502 Cart: somewhere, third or fourth, I would guess. So. This is based on data from 2,020.

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* Kresge 502 Cart: As I mentioned, the the burden of where cancer is occurring in the globe, differs by the type of cancer and on the on the left. This is just what percent of cancers are occurring in each region. And then on the right is cancer-specific deaths. And what you can sort of see is that there are. There's variability in the incidence and mortality where they're happening across the globe.

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* Kresge 502 Cart: And this is just a kind of a, a brief introduction on each of the cancer specific chapter talks. And then also, when you work on your group projects, this may be something to delve into. Where is my cancer occurring across the world? What are the populations now that have the greatest burden? And where is it gonna be happening in the future. So one of the databases that you're gonna get to use for group

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* Kresge 502 Cart: projects, allows you to estimate where in the future cancer, incidence and mortality may be happening. So today, as we mentioned, 19.3 million new cases in 2,020 almost 10 million cancer deaths in 2,020 in 2040 is expected to go to 30 million new cases

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* Kresge 502 Cart: and 16 million cancer deaths.

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* Kresge 502 Cart: Take a minute. Why and talk about why.

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* Kresge 502 Cart: what factors might explain the total expected number of cancer cases and deaths? And are there some specific parts of the world, that we might be most concerned about

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* Kresge 502 Cart: once.

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* Kresge 502 Cart: What were some of the things that that you were thinking about in terms of? Why, the total number of new cases and number of deaths from cancer is expected to increase so much

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* Kresge 502 Cart: in 20 years.

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* Kresge 502 Cart: So one of the reasons we were saying, Yes, exactly right. And so there! And we'll talk about that in a moment. But there's parts of the world where the aging of the population is happening much faster than it is in in the Us. We even lost years of life recently. I think we just caught up again. But you're right. I think the aging of population, certain parts of the world is really gonna have a big effect. Some people over.

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* Kresge 502 Cart: Yes, yeah. Maybe it could be diagnosis methods improved. For example, it could be diagnosis in the earlier stage of cancer.

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* Kresge 502 Cart: Yeah, no, that's a really interesting idea. So in a kind of related to that. It could be a couple of different things. One is. There's populations where some types of screening have generally not been done that may be starting to screen. So, for example, screening for prostate cancer with Psa may start to be done in parts of the world where it had been done. And you're gonna be diagnosing something called what we call pseudo disease, which are cancers

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* Kresge 502 Cart: truly cancer. But the only reason they came to light was because of screening, and then there may be coming down the road. early detection of cancers that we've never had screening before. That also may be increasing the incidence.

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* Kresge 502 Cart: Yeah, no, there's so many different types of exposures that are gonna be happening like you said environmental exposures. I think there's also, there's gonna be places where that had

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* Kresge 502 Cart: in general, like, you know, parts of Southern Europe, for example, that used to have healthier Mediterranean cell diet that are leaning more towards Western style diet. You're also seeing that epidemiologic transition in other parts of, say, in Africa, for example. So those things may be contributing to as well. And so I think it goes to this idea. Any anything else? Yes, definitely, right? Exactly. That's happening across the world.

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* Kresge 502 Cart: And population increase. Exactly. Right? Yeah, exactly. So. All of those things have gone in. And probably in these calculations, I bet they're relying more on population, growth, and aging of the population. But I think these are all things we need to be thinking about above the increasing burden of cancer.

31:06

* Kresge 502 Cart: so this video just kind of shows how I'm not going to pull it up now just in the interest of time, but really shows the changing of aging and structure which is happening much more so in areas of the world where infectious diseases, for example, used to be common causes of early death, where childhood mortality was higher.

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* Kresge 502 Cart: Those things now are lower, so people are living longer and eligible to develop cancer and die from cancer. So each year the American Cancer Society puts out statistics. And this is something. Also that you'll be looking at for projects on the burden of cancer. Ed was just recently awarded a research professor at the American

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* Kresge 502 Cart: Cancer Society, which is a very prestigious award congratulations.

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* Kresge 502 Cart: So based on the newest data and based on projections, it's suspected that about 2 million people are gonna be diagnosed with cancer in the United States, little more men than women. 611,000 deaths due to cancer. Because we talked about number, prevalence of cancer.

32:25

* Kresge 502 Cart: Well, the prevalence of cancer survivors. And that's that definition is complicated a little bit. But by what? What American cancer society means and what other people mean when they talk about. This is anybody who's alive after a diagnosis of cancer is considered a cancer survivor.

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* Kresge 502 Cart: currently, in the United States over, actually, I think the number now is over 17 million people are living as cancer survivors. Lifetime probability of cancer is about 39% women and 41% men.

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* Kresge 502 Cart: So one of the things there's a great article if you're interested in. You know all of the cancer statistics that we collect rely on the quality of the databases that collect the information. There's some parts of the world where they capture mortality data pretty well, but not in cancer incidents. There's other countries.

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* Kresge 502 Cart: For example, in Scandinavia, which we talked a little bit about, where it's actually mandated by law that all cancer diagnoses are reported at the national level. So there's a lot of variability in standardized ways of collecting that information, timeless timeliness of reporting, completeness of reporting, and how much of the population is captured. There's for example, I think, in in parts of China

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* Kresge 502 Cart: there's really good cancer registries that cover a subset of the population. But other parts of the country in which there's not as good capturing, and also in Africa as well. I think we have those issues as well in this country versus this country what I might be concerned about the quality of the registry of those.

34:12

* Kresge 502 Cart: And these are the the main data sets that you're gonna use. So globally, the International Agency for Research on cancer. Puts together. national databases together. You're gonna use it for your project. It's really amazing. The web interface you can use. The cancer atlas has really great graphics.

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* Kresge 502 Cart: That you may wanna take a look at through group projects. And then in terms of data from the United States American Cancer Society, for example. And you'll be using these as well uses. Something called this surveillance epidemiology and end results program or seer program.

35:03

* Kresge 502 Cart: So

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* Kresge 502 Cart: and II was gonna do a breakup. But I want

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* Kresge 502 Cart: and to be able to have some time. Oh, does not like that.

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* Kresge 502 Cart: Go ahead.

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* Kresge 502 Cart: Well, I'll instead of having you guys do it as a breakout. I think we'll do it together. So if you have

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* Kresge 502 Cart: your own laptop with you. Click on that link which will bring you to the global can data set.

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* Kresge 502 Cart: And let's walk through this thing together. So I want to look at today. What are the most common incidents and mortality rates for cancer globally, and make some comparisons between men and women. So to do that. I clicked on the link.

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* Kresge 502 Cart: What we want to do is to click on the link for cancer today.

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* Kresge 502 Cart: And then after that, you want to click on the multi bars. Tab

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* Kresge 502 Cart: multi-bars tab here

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* Kresge 502 Cart: and then first we wanna look at cancers in all men and women, and then we'll look at men and women separately. So here we have

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* Kresge 502 Cart: both men and women here. These are going to rank the cancers based on incidence.

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* Kresge 502 Cart: So if you look across everybody and across everyone in the world. The most commonly diagnosed cancer is breast cancer, prostate cancer. Second, lung cancer is third, colorectal cancer, fourth, cervical cancer ranks. Fifth, and I think this is really unfortunate. Given how much we know about prevention

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* Kresge 502 Cart: of cervical cancer through through screening right? So screening to identify cancer lesion before it becomes cancer, and then kind of getting rid of it as well as through vaccination for Hpv. Vaccination

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* Kresge 502 Cart: stomach cancer. Also, if you, if not be without looking at it. Don't don't click. If you had to guess. What do you think are the top 3 mortality in both men and women from cancer cancer mortality. So top 3 or 4 just yellow. Some cancers top

37:28

* Kresge 502 Cart: for mortality, mother.

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* Kresge 502 Cart: this is gonna be both among men and women. I should say, neither the Us. Nor the international databases have people where they're able to identify people who don't identify as non-binaries.

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* Kresge 502 Cart: It's one of the limitations of data. So lung cancer, mortality, colorectal cancer.

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* Kresge 502 Cart: Excuse me, skin is interesting. So most or mid, I won't say most. But many of the registers report melanoma. But don't report other types, squamous or Basil so and mo, and part of that is because those are. They're probably very high incidence, but not high mortality. So

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* Kresge 502 Cart: so skin is probably not going to pop up for mortality stomach. That's something we think a lot about here. and the Us. Been a big burden, not internationally. Thank you at it.

38:43

* Kresge 502 Cart: Anything else. Well, let's let's look together. So I'm going to click off of incidence and click on mortality.

39:02

* Kresge 502 Cart: Lung cancer rings, first, breast cancer, mortality rings, second, colorectal cancer, liver cancer.

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* Kresge 502 Cart: So let's see where liver cancer ranked in terms of incidence, liver cancer was a little bit lower here, but because it's so highly fatal in terms of mortality rates per 100,000. It ranks quite high and then prostate. Cancer is pretty close to stomach cancer.

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* Kresge 502 Cart: and then, if you what you can do also, you can do some interesting, direct comparisons of incidence to mortality. You have some cancers like liver cancer, we can see the incidence almost mirrors mortality.

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* Kresge 502 Cart: whereas you know, prostate cancer.

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* Kresge 502 Cart: Many people with prostate cancer died with their cancer, but not from their cancer. So you can really get a sense of comparing this. The other kind of comparison you could say is, let's look at incidence, and let's look at comparisons of

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* Kresge 502 Cart: I thought you could do this. Think that there is a way to do this.

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* Kresge 502 Cart: anyway. There's a way that you can do this where you can compare men and women on the same figure. I'll I'll follow up with it to show you how you can do that. So, anyway. So I think you'll learn a lot about your specific cancer. And then, as you bring it presentations together, and then when you present to the groups. You'll hopefully, I'll learn a lot. So just in terms of the United States and then I'm gonna see, I'm gonna just do these last

40:16

* Kresge 502 Cart: 4 slides quickly in terms of the United States. Pancreatic cancer was something someone mentioned in terms of mortality. It's alarmingly high in the United States for mortality it's become for men the fourth leading cause of cancer, death, and for women the third leading cause of cancer, death.

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* Kresge 502 Cart: part of that in terms of its ranking. It's coming up both because

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* Kresge 502 Cart: breast and prostate cancer rates have been going down for some time, and pancreatic cancer will see here. There's a suggestion. It's sort of this pale blue line is coming up in incidence slightly over time. So these are the mortality curves over time. You can see. What do you think happened?

41:10

* Kresge 502 Cart: What's happening? What what do you think is leading to this huge decline here? When do you think people stops big smoking cessation? Things started happening in the United States. You had to guess. So peak is around 1,990.

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* Kresge 502 Cart: When do you think people like for men smoking cessation happened. We talked about the lab

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* Kresge 502 Cart: you have to guess.

42:01

* Kresge 502 Cart: Yes, exactly. Yup, exactly. So. Given the lag of what it takes for when someone smoking to. When you see mortality, you're starting to see the reductions happening in the late mid to late. So, therefore, smoking cessation in men probably started in the late. What about women?

42:02

* Kresge 502 Cart: What are you saying in terms of the timing of when

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* Kresge 502 Cart: the increase happened? And then, when the decrease happened? What do you think the reasons are we'll go into this in a lot more detail.

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* Kresge 502 Cart: Women started smoking much later than me did, and as a result they're starting to stop smoking later than men did. So it's big issue. Okay, this is gonna be my final side. And I'm gonna pass it over to Ed. So II mentioned this briefly. But there's a large difference in both incidence and mortality of cancer, by sex. And so for 35

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* Kresge 502 Cart: different cancer types that are shared between men and women. 30 of them.

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* Kresge 502 Cart: The incidence is higher in men than it is in women, the one cancer that is higher in incidence. It's up there. I think the one cancer that's higher in women than it is in men is thyroid cancer.

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* Kresge 502 Cart: Some are kind of similar. So about 4 of them are kind of similar. This particular study used an ecologic approach and tried to adjust for differences, say, in smoking, so smoking is a risk factor for many cancers.

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* Kresge 502 Cart: and in many populations men are more likely to smoke than women. So say, Okay, can we take away the effect of smoking? Do we still see an increased risk for many of these cancer? The answer was, yes. The other factor they tried to take into account again, is an ecologic study. So not independent observational data where you had confounding control but just for alcohol. And still there was this high excess risk

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* Kresge 502 Cart: of cancer. So there's been a lot of research into try to understand what other factors might be explaining this excess risk.

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* Kresge 502 Cart: Okay, so with that, I'm gonna end there and

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* Kresge 502 Cart: so I'm gonna click here and then

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* Kresge 502 Cart: absolutely share it. Sorry. Stop sharing alright.

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* Kresge 502 Cart: Sorry.

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* Kresge 502 Cart: I feel like when I'm with my son. And my phone's not working. And he's like, did you turn it off? I'm like, I turned it off. Something happens.

45:01

* Kresge 502 Cart: Okay, you should be up. Okay. Thank you so much.

45:16

* Great. Thank you

45:22

* Kresge 502 Cart: thanks, Laurel. That was great, see. So I know some of you were in my cancer course. So magic trick the whole course. 45 min.

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* Kresge 502 Cart: But I'll try to cover today. And actually, since

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* Kresge 502 Cart: since I'm also teaching Thursday on obesity, physical activity, I probably won't get through all of these. So maybe the first 3 and I I'll continue on Thursday. So okay, so this is kind of the outline that why is that believe to be important for cancer

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* Kresge 502 Cart: and then so it's a little bit of a historical perspective. And then what type of evidence should be prioritized to study died in cancer. Laurel. I alluded a bit like, you know, randomized trials.

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* Kresge 502 Cart: the aspirin, and we'll see that that was actually a nice analogy for what we'll see. And then very, very quick, basic, nutritional epi, how diet is assessed, because for nutrition and cancer.

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* Kresge 502 Cart: you know, the assessment is is so important, you know, smoking and cancer, like, you know, we think we can assess smoking pretty well, but the diet is very

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* Kresge 502 Cart: difficult to assess, and, in fact, you know, what do we mean by diet? Let's

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* Kresge 502 Cart: thinking very broadly here. So obviously, diet is important for things like growth, and body weight. So so that that's under energy balance. And actually, I'll talk about that mostly on on Thursday but keep that in mind. So so diet copies is a lot of things, and we can think of diet terms of broad dietary patterns.

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* Kresge 502 Cart: Mediterranean diet, or like an inflammatory diet pattern which I'll talk about.

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* Kresge 502 Cart: You know a lot of traditionally, a lot of focus has been on like macro nutrients like fad carbohydrates, you know. I'm sure you hear a lot, you know, in your daily life like low carb things like that.

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* Kresge 502 Cart: I have alcohol all here, but we could think of alcohol separately. Sometimes you could think of it as diet, or just separate and then there's micro nutrients vitamins, you know, vitamin, e and antioxidant. But we'll talk about minerals, calcium and then there's phytochemicals. And and by these I'll give an example. But

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* Kresge 502 Cart: these aren't technically nutrients, you know, like with nutrients, you you like essentially need it. That's the, you know, essential nutrients fibre. Chemicals are things like that you can get. For example, fruits and vegetables. They're antioxidants. They're technically not nutrients. And I think fiber is in there, too. I mean, most of us know fiber is important, but it's not something that's 100% essential

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* Kresge 502 Cart: for for survival

48:47

* Kresge 502 Cart: and then there are other aspects of diet like, we don't think of carcinogens in general. But for example, when you cook meat particularly red meat, or you're not the kinds of me. You make compounds that are carcinogenic studies. And then, like contaminants, you can think of things like mercury and fish. There's a lot of

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* Kresge 502 Cart: things that you know. Obviously you don't want mercury, but it gets into fish, for example.

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* Kresge 502 Cart: and contaminant. II should also put like additives, for example, artificial sweeteners. In fact, there was like some of these public polls where they asked people like, What do they think our report for cancer? I mean smoking makes it to the list, at least for most people. But then people actually put things like artificial sweeteners ahead of like obesity.

49:21

* Kresge 502 Cart: A lot of people don't mention body weight or things like that, but they'll they'll mention things that you know where the evidence they're interesting. But the evidence, maybe, isn't that strong?

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* Kresge 502 Cart: Okay? So I think

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* Kresge 502 Cart: it's really important. I mean, you might say, well, I don't want to know all this history, but I think it's makes it easier to understand a lot of things that are going on. If you, if you look, take a little bit of historical perspective.

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* Kresge 502 Cart: So in in so 1,000 981,990 already, then there was a lot of interest in diet and cancer. But most of the evidence at the time were like animal studies, mechanistic kind of studies. Then the ecological studies, secular trends, migration studies

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* Kresge 502 Cart: and right around the time of 1980 S. Case control studies began to emerge, and then cohort and randomized trials came a little bit later. So I've marked animal ecologic studies up. Just give you a little bit. And Lorelei, you know.

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* Kresge 502 Cart: alluded to some of this. So this is a study. I mean, this has nothing directly to do with diet. But these are colon cancer rates from 1,964 to 1,995 these are men and women. These lines here are Uk, United Kingdom. This is

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* Kresge 502 Cart: Japan. The as you could see men and men and women were about 5, at least 5 times lower than the UK. 1,964. Then they went up a bit pretty in parallel, and then particularly, men really took off, and so rates. So they went from about fivefold lower to twice as high, particularly men.

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* Kresge 502 Cart: which is dramatic, a dramatic change in about 3 decades.

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* Kresge 502 Cart: You know. In fact, even if you start from 1,970, it's almost like a 2 decade of incredible increase tenfold increase in rates. Now,

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* Kresge 502 Cart: Dr. Song, Mignon will get into some of the specifics for colon cancer. So I don't want to get, you know, like, why are the male rates higher?

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* Kresge 502 Cart: We'll get into some of that. But the key point is that

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* Kresge 502 Cart: cancer can, particularly colon cancer rates can change dramatically. And now what could accounted for this? Well, you know, smoking alcohol could contribute in part to to the men but smoking and alcohol is won't contribute for many to cancers in in Japan. And so so there.

52:18

* Kresge 502 Cart: yeah, it's it's not doesn't directly link a specific dietary factor. But it's believed to be related like you kind of rule out like what else could explain this? And so so diet is, is sort of implicated indirectly.

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* Kresge 502 Cart: Now th, there are other evidence, and these are like the ecologic studies. I'm sure all of you have ep courses, and you're not supposed to infer causal associations. And so I. This is looking at dietary, fat and breast cancer, death rate, or incidents with pretty much the same and you see this pretty strong correlation across countries.

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* Kresge 502 Cart: And this was.

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* Kresge 502 Cart: this is probably around 1,970, because I noticed. Japan is actually low here, too, but it's probably a bit higher now. But in any case there's a very strong correlation between fat intake and breast cancer mortality.

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* Kresge 502 Cart: And now, you know, I actually 1975.

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* Kresge 502 Cart: Now, at the time, actually, there was people really did jump onto. Oh, it must be fat in 1,900 sixtys and seventys like fat, was dietary. Fat is is the, you know.

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* Kresge 502 Cart: the bad actor. Everybody attribute everything to to fat, and we don't quite agree as much these days. But in any case but it was, you know, something correlated with fat intake so it again. I wouldn't for a causality, but it just shows that there's something probably related somewhat to diet

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* Kresge 502 Cart: accounting for this.

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* Kresge 502 Cart: Now there was a lot of interest in in fruits and vegetables, and there are actually lot thousands of potential compounds that may be beneficial case control studies particularly indicated

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* Kresge 502 Cart: inverse associations with fruit and vegetable. And so there are other things like carotenoids laurel. I mentioned lycopene, which is in tomatoes, which is an antioxidant. Ii just just for illustration that there, there are a lot of poly females, a lot of compounds that kind of look like this

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* Kresge 502 Cart: like, and

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* Kresge 502 Cart: and they concentrate in certain foods. So, for example, like, let's say, flavinomes.

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* Kresge 502 Cart: I'm not sure they're important, but let's say they're if they're important, then citrus fruits are are this, you know the main sources that people eat a lot of citrus fruits get get a lot of these.

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* Kresge 502 Cart: So why is it important to get a lot of these compounds.

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* Kresge 502 Cart: You know, it's a little bit unclear, but but there are lots of studies. And you know, people make

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* Kresge 502 Cart: like whole academic careers focusing on, you know, one or few of these compounds

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* Kresge 502 Cart: and these have a lot of bio active properties particularly related to cancer. So don't you know, you don't have to memorize the slides. Just just kind of to illustrate that you find lots of compounds. They're concentrated in certain foods that have all these effects, like our OS. Scavenging is like reactive oxidants species. So that's like antioxidants.

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* Kresge 502 Cart: They affect lots of things in the carcinogenic process, and a lot of these are based on in vitro studies. But they're also like animal studies.

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* Kresge 502 Cart: You know, like, for example, eg, cg, is, it's in green. T. Primarily forget. I can't pronounce the full term. But, eg. Cg, it's a very

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* Kresge 502 Cart: highly interesting compound. II remember some years ago hearing talk about some of who study this. And then animal studies, just EGC. Like. The the studies are so impressive they gave certain amounts of completely like prevented tumors, and they looked at things like pathways, like angiogenesis, completely block blood vessel growth and tumors.

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* Kresge 502 Cart: So these are very interesting. Now, you know whether they're important in people is questionable.

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* Kresge 502 Cart: Here. We focus more on epidemiologic studies or clinical trials.

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* Kresge 502 Cart: But this is just to give you a spectrum of things.

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* Kresge 502 Cart: Now, as I already mentioned, the dietary fats. So this was a study published in 1,990, and

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* Kresge 502 Cart: so I just

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* Kresge 502 Cart: took a few sentences from the abstract. So we conducted a combined analysis, the original data to evaluate the consistency of 12 case control studies of valued in breast cancer. Our analysis shows a consistent, statistically significant positive association

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* Kresge 502 Cart: between breast cancer, risk and saturated fat intake and postmenopausal women relative risk 1.4 6 highly significant. And this study, along with other evidence like the ecologic stimulated this very massive women's health initiative, randomized randomized trial of a low, fat diet and breast cancer.

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* Kresge 502 Cart: So there weren't prospective data at the time. Not much prospective data at the time.

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* Kresge 502 Cart: So

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* Kresge 502 Cart: and I'll get back to that now in 1,981 Don Peto, or 2. Well, Peter, still alive, Dr. Dala

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* Kresge 502 Cart: died about 10 years ago or so. They're very, very prominent epidemiologists, you know. Doll is probably the person most responsible for making the link between tobacco cancer

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* Kresge 502 Cart: and

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* Kresge 502 Cart: they they came up with this estimate of attributable like, this is based. This is supposed to be for the United States. So percent of cancer deaths

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* Kresge 502 Cart: that are trivial to to various factors so so that. I think, laurel. I talked a little bit about this last week. So so, for example, tobacco, they estimated that at the time, like around 1,980 in the United States. 30% of cancers all cancer mortality would be prevented, preventable if everybody like

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* Kresge 502 Cart: and stop smoking or or didn't smoke. And of course there's a latency issue, too. So have maybe people did smoke for 20 years, the last one. So so that's and and then they had, like a range of plausible estimates.

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* Kresge 502 Cart: And

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* Kresge 502 Cart: what's really striking, and I think a lot of people were struck by this is that they had this very high estimate for diet.

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* Kresge 502 Cart: 35%, but also a very wide range.

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* Kresge 502 Cart: Now

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* Kresge 502 Cart: these, how do they come up with these estimates?

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* Kresge 502 Cart: th, they were. There's very little direct data. And and they they admitted this. I mean, they they were very like upfront about this. But the type of data that they use is is a little bit more like a inferring like, I'll just go back a few slides. So so, for example, like, you know.

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* Kresge 502 Cart: again, this is looking at fat and breast cancer, and don't even focus so much on the fad here. But you see, this wide variation in cancer rates, right?

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* Kresge 502 Cart: And so the US. Is up here.

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* Kresge 502 Cart: Assuming that this isn't all due to genetics, and there's reason to think that they're not in theory. The US. Can, you know.

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* Kresge 502 Cart: can get down here in theory, like.

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* Kresge 502 Cart: maybe it's a reduction in fat intake. Maybe it's something else. But there's there's something probably related to diet. And then, you know, if we go back one slide.

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* Kresge 502 Cart: this indirectly shows you can make a change, I mean. Fortunately, in Japan. They went in the wrong, the wrong direction. They it's probably because they took up the western diet. They had a big increase, right? But the the point is that most a large number of cancers are preventable and they attributed a lot to diet. But they said, there's a really wide range of uncertainty.

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* Kresge 502 Cart: and this is a quote from their paper

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* Kresge 502 Cart: said, it may be possible to reduce us cancer death rates by practic practicable dietary means by as much as 35 maven use the word guesstimated as stomach and large bio

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* Kresge 502 Cart: 90%. So so then they made some estimates for specific cancer types. So so like the stomach and Colon, they had the highest estimate

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* Kresge 502 Cart: kind of makes sense gi spectrum.

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* Kresge 502 Cart: And then they said, although this figure of 35 is a plausible total. The parts that contribute to it are uncertain in the extreme.

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* Kresge 502 Cart: And they also listed potential mechanisms. So why is diet important and you know, they there was actually very little data at the time on things like obesity, energy, balance, fiscal.

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* Kresge 502 Cart: But they did know one of the mechanisms where it was like potential like over nutrition.

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* Kresge 502 Cart: Like as as nutrition gets better in population.

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* Kresge 502 Cart: Just yeah, like laurel. I just had a slide on height like, you know, the population average height goes up agent. Manarchy go goes down, and and those are risk factors for cancer. That may be. I mean, it's

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* Kresge 502 Cart: it's hard to think of plaza, or at least practical public health. But it's important to know, like, at least to explain why cancer may be affected by things like nutrition. So so some of it may may be this early life exposure, like affecting the agent, monarchy or height, and that might be related to like things like growth. So

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* Kresge 502 Cart: They were so precious, I mean, I remember, like in their paper they they said like, well, there isn't much evidence for over nutrition, except for endometrial cancer at the time, but like, we wouldn't be surprised in the future if more studies more evidence emerges on the importance of over nutrition, which is exactly what what turned out

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* Kresge 502 Cart: but they also had these other mechanisms that, like looking at things like carcinogens, like things like I like I mentioned, if you cook me

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* Kresge 502 Cart: at high temperatures, you produce these carcinogenic type

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* Kresge 502 Cart: things, and then things like promotion. So one statement that they made here that I think, really had a big impact on the field.

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* Kresge 502 Cart: and it made sense at the time, and it made

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* Kresge 502 Cart: it's questionable whether it turned out to be true, but it says any of the punitively protected nontoxic vitamins trace elements, micronutrients protease inhibitors or antioxidants

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* Kresge 502 Cart: that finish up in the top. 12 hypotheses might just be testable.

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* Kresge 502 Cart: as might intake of various putative, influen protected types of fat or fiber. So there's what they were saying, and it might be a little confusing. But so so they said, well, let's list all the important, you know, plausible hypotheses like antioxidants like that, and then they propose doing like some a bunch of randomized trials, or like 10 or 15 randomized trials.

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* Kresge 502 Cart: And you know they were saying, like with high confidence. Oh, you know, if you do like vitamin, a like that will be the one. But let's pick like 10 or 15, and then do randomized trials, and then, if one of them hits, if one out of 10 hits.

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* Kresge 502 Cart: that's great, you just help, you know the population to eat more of that, or even do fortification or supplementation.

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* Kresge 502 Cart: So that's how the field kind of was thinking at the time.

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* Kresge 502 Cart: And so for the

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* Kresge 502 Cart: actually that that gets into this next part, which I'll talk about is is that you know it does make sense. If you're focusing on a micronutrient why not do a randomized trial. Right? That's you'd get a very definitive answer

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* Kresge 502 Cart: potentially

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* Kresge 502 Cart: I'm sure most of you have seen something like this where the hierarchy of evidence where we have randomized trials of top. And then cohort studies, case control studies, etc.

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* Kresge 502 Cart: And oh, I'm sorry. Yeah, yeah.

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* Kresge 502 Cart: sure

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* Kresge 502 Cart: this one or this one. I don't understand hypotheses.

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* Kresge 502 Cart: Yeah. They. Yeah, right? It's probably would make more sense if I had more of that. But

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* Kresge 502 Cart: basically what they were saying they were arguing is like like, let's make a list of the like. Let's say, Micronux, into vitamins that have the most support. I mean that none of them were definitive, obviously at the time.

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* Kresge 502 Cart: And then, but based on other evidence, like animal studies or case control studies like you know, which compounds have support that they may be beneficial against cancer. And then let's do

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* Kresge 502 Cart: 12 randomized trials, separate randomized trials to test to test these and get a definitive answer.

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* Kresge 502 Cart: What is potato's teeth?

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* Kresge 502 Cart: Tha tha, that's just a a type of compound th there were. It's a it's something found in specific vegetables that would believe to be important for our cancer at the time. But that's it's not important. Just that's just one of the compounds. There was a lot of interest. There's not much interest

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* Kresge 502 Cart: that I know

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* Kresge 502 Cart: nowadays. It's just a compound like that may have anti-cancer effects.

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* Kresge 502 Cart: That's part of all the micronutrients in that child exists.

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* Kresge 502 Cart: Yeah, there's I forget exactly how they work like they they block

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* Kresge 502 Cart: certain kinds of enzymes

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* Kresge 502 Cart: that I forget exactly why this was popular 19 eighties and nineties that that they might have anti-cancer things. But but the bottom line is, let's just find a bunch of compounds

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* Kresge 502 Cart: and then do randomized trials.

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* Kresge 502 Cart: And so I won't spend a lot of this. I mean, most of you know that randomized trials are considered most reliable type of evidence when you could do it.

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* Kresge 502 Cart: But you know, realistically, most of the evidence is from case control and cohort studies.

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* Kresge 502 Cart: But and laurel. I alluded to this in the previous her talk that

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* Kresge 502 Cart: you know. Yeah, randomized trials are great and you could do it. But there are issues like.

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* Kresge 502 Cart: For example, latency is one of the issues that we'll talk about

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* Kresge 502 Cart: and that, you know.

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* Kresge 502 Cart: people like, if you're thinking about therapeutics. And most like medical doctors. You know, they want very specific knowledge, like, what drug? What do when to give it? And and what effect will it have on the disease, and in that case you almost always have to do a randomized trial. There's almost no way around it. But if you're looking at, you know, diet

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* Kresge 502 Cart: and cancer life course, eating like fruits and vegetables like over your entire life.

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* Kresge 502 Cart: Does that have an impact on cancer that that might be harder to do a randomized trial.

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* Kresge 502 Cart: So

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* Kresge 502 Cart: II just have make a list here. You can probably add it, add to it, or subtract or think of other things. But

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* Kresge 502 Cart: you know, when you're thinking about diet and drug therapy, you know

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* Kresge 502 Cart: conceptually what you think is like, okay, you're designed to treat a specific condition, and the effect of the drug is for a specified time period, you know, antibiotic. You give it for like 5 days or a week.

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* Kresge 502 Cart: The default is no drug. I mean, it's either drug or no drug.

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* Kresge 502 Cart: There's little other data to consider like ecologic data things like that. You would only get a drug. If you the benefit is anticipated, you wouldn't test. You wouldn't test like something that you think is toxic in a randomized trial. So it's only a benefit, obviously.

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* Kresge 502 Cart: And double blinded study is feasible in most cases

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* Kresge 502 Cart: for diet and cancer. Yeah, randomized trials would be great if you can test everything but

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* Kresge 502 Cart: a diet is very different. First of all, it affects other

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* Kresge 502 Cart: cancers. Or, you know, if you're focused on colon cancer. But you know, diet can also affect other cancers and other diseases. We already know some diet factors that are

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* Kresge 502 Cart: that are good for heart disease. So you have to take that into account. You can't ignore that information for ethical reasons. For example, the effect can be over. Life course can be over many years.

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* Kresge 502 Cart: It's hard sometimes to do like a placebo control. Default is well, you know, like what's a diet? It's not like you have diet or no diet. You have a different diet. So even like what the control group is is different

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* Kresge 502 Cart: other relevant data like sometimes. That are that are useful. They won't give you the the full answer. But, like, for example, the ecologic data do inform sometimes on dietary hypotheses, but usually don't form drug therapies. You have a new drug tested before. Not all aspects of diet people in the pill. You you can only do a micronutrient type of stuff you can't

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* Kresge 502 Cart: like. Do you know, even like, for example, if you do a high, fat intervention.

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* Kresge 502 Cart: or low fat, you know, people are probably gonna know. So it's not double blind. So diet and cancer, you know, it's very difficult. Now, having said that. So so actually, there have been attempts to have like these

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* Kresge 502 Cart: big changes in the diet like low, fat diary pattern. And those studies had very big issues with compliance.

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* Kresge 502 Cart: It's very hard to get 30,000 people to have massive changes in your diets like for 1015 years. It's very practical. But let's ignore those for now and focus. Well, how about the micronutrients? How about something you can give like that.

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* Kresge 502 Cart: Even those I mean, those are important. And they have been important studies. But even those have have limitations. And I'm going to talk quickly about 4

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* Kresge 502 Cart: limitations. I listed 6 here in total. I mean, obviously, there are potential issues in trials. The study isn't large enough, or the adherence is low.

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* Kresge 502 Cart: particularly relevant if you're trying to have change the whole dietary pattern.

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* Kresge 502 Cart: But even if you're just focusing on something, you can actually put in a pill like a vitamin.

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* Kresge 502 Cart: There are lots of issues that that

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* Kresge 502 Cart: could lead you to get the false or misleading answer

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* Kresge 502 Cart: so the first thing I'll just mention. And actually, this is very similar to what laurel I was talking about.

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* Kresge 502 Cart: Cancer occurs in stages, and

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* Kresge 502 Cart: you know this is sure to some degree simplify, but I think still useful. So you have like initiation

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* Kresge 502 Cart: where you where you get normal cells and cause DNA damage doesn't get repaired. But even that's far away from cancer. That's like the first step. Then you have things like promotion that cause clonal expansion. You get like more mutations and finally get a benign tumor and eventually fewer them will progress to cancer. So it's a very

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* Kresge 502 Cart: has like different stages.

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* Kresge 502 Cart: So here's like an example. This isn't trial data. This is observational data. Actually, the nurse's health study.

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* Kresge 502 Cart: When you look at colon cancer and years of multivitamin use of.

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* Kresge 502 Cart: you see, like not much going on, certainly, after one to 4 years, and then perhaps

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* Kresge 502 Cart: suggested a not significant reduction like 5 to 14 years, but then a clear lower risk. After 15 years. This looks a lot like the slide that Lori showed for aspirin

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* Kresge 502 Cart: colon cancer, which was a randomized trial. So in that trial people started taking aspirin so if if you have like 2 groups, one takes aspirin and takes placebo, follow them, for you know, like a number of years, you see no difference

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* Kresge 502 Cart: up to 10 years. So if you stop the study at 10 years and say, Oh, aspirin does nothing.

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* Kresge 502 Cart: and then after but you keep following them up to me, say, Oh, okay. Now, aspirin is protective. So, for example, if

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* Kresge 502 Cart: if you you know, think of this like multi-stage process.

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* Kresge 502 Cart: if you impact, if you have something that only protects against initiation but doesn't affect promotion.

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* Kresge 502 Cart: it's going to be a while to see an effect, because, like one way, I think the simplest way that that I can think about it is so. So let's say, like.

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* Kresge 502 Cart: If you're looking at a 60 year old. So your population, everyone is 60 who's going to get cancer at that point? So now, the people that are going to get cancer at age 60.

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* Kresge 502 Cart: They probably already have gone through a lot of these processes. So the ones, if you can look, I mean, this may be hard to do. I mean you can do it sometimes like, for example, colonoscopy. Essentially does this.

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* Kresge 502 Cart: If you look at precursor lesions right like some, have already gone like like too far along the process. So, in other words.

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* Kresge 502 Cart: like

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* Kresge 502 Cart: in the last 10, like, let's say so at age 60 the cancers that show up at age 60,

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* Kresge 502 Cart: all of them already had had their initiation by age 50. Let's say so. If if you have

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* Kresge 502 Cart: so the cancers you're going to see at 60, like the last.

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* Kresge 502 Cart: the previous 10 years have have nothing to do with initiation. So so, in other words, even if you for 55 year old, like, if you prevent initiation. Yeah, maybe you'll prevent a cancer like when you're 65, or 70. But you're not going to prevent a cancer that they're going to have at age 60.

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* Kresge 502 Cart: They're already too far locked across this. So so that's that's a really important thing for cancer. Because.

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* Kresge 502 Cart: you know, that's why the randomized trials often like Don't get the answer you expect. It's because they really haven't gone long enough.

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* Kresge 502 Cart: Very few randomized trials go beyond 5 or 10 years that makes sense to people.

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* Kresge 502 Cart: Yes, it's just another question. I don't know if you have come closer.

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* People who have children at a later age since you mentioned that

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* Kresge 502 Cart: these cancers

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* Kresge 502 Cart: developments in the initiation started on 50.

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* Kresge 502 Cart: So, for instance, someone had children at age 55,

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* Kresge 502 Cart: is it possible that their mutated genes for the child. At an earlier age they will have less damaged genes in later age. Older.

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* Kresge 502 Cart: Yeah. I, for instance, the genetic makeup would have less stress and less.

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* Kresge 502 Cart: There, there! I think there is some evidence for for childhood cancer. Like I think II don't maybe lower life, or someone knows better like for some Leukimius, that, like age of like the father, I think older age would have a higher risk of that, so some of it right could be

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* Kresge 502 Cart: but that's like the right. So so that's another. I mean, that's a related but another issue, like in terms of what's passed on the term line.

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* Kresge 502 Cart: But even like, like, so for example, when we think of, let's say, like, prostate cancer, you think like Bob, well, it's old men get prostate cancer.

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* Kresge 502 Cart: Yeah, like, that's probably true in most cases. But the initiating event may have happened at age 12.

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* Kresge 502 Cart: So like, you might have like cells like like puberty seems to be important for prostate and breast cancer.

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* Kresge 502 Cart: So you might have, like some initial things that go on

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* Kresge 502 Cart: like a puberty may may give some people, let's say, like early puberty, for example, might give people, let's say, twice the number of initiated cells than another person.

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* Kresge 502 Cart: but they're still far away from cancer. So you have

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* Kresge 502 Cart: twice a number of initiated cells, and then over the next 50 years, lots of things have to happen, exposed the estrogens. Things like that. But the group that starts with twice as many initiated cells probably is going to have twice the risk of cancer.

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* Kresge 502 Cart: least as a group, not individually, obviously, doesn't mean that they're gonna get cancer. But but the it's it's really hard, like for some people to unders, you know, understand this, because they see? Well, the cancer happened like at age 70, like, what did I do last year? That gave me the cancer?

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* Kresge 502 Cart: It's, you know, may may have been last year, but it may have also been 50 years ago. You know, it's not like an infectious disease, like, you know, we get a cold like. We don't say gee! What was I exposed to in 1992? That caused my cold? No, Dick, like, who was I sitting next to like yesterday?

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* Kresge 502 Cart: But for cancer. The timescale is decades.

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* Kresge 502 Cart: Another issue is, you know, I think Dr. Sam will talk about this more. So don't focus too much on the example, just to to illustrate. So this is calcium intake and

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* Kresge 502 Cart: colorectal cancer. And you can see that there is a inverse association, right? So that

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* Kresge 502 Cart: the this is a pool analysis of 10 forward studies. So starting from low calcium intake as you go high, the risk gets lower, and then it levels off right?

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* Kresge 502 Cart: And it's hard to write the exact

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* Kresge 502 Cart: like W. Where there's a risk level off. But let's say it's around here somewhere, so clearly, if you go, if you're too low. Get benefit when you reach here. If you're like a 1,300 milligrams today, going to 2,000 doesn't seem to be that beneficial right?

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* Kresge 502 Cart: Okay, so let's assume that this is the true dose response. And this is from observational study.

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* Kresge 502 Cart: Now, like, there was a randomized trial actually, that women's health initiative one can. They also had a fat they also want for calcium.

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* Kresge 502 Cart: and they gave it a women. These are plus menopausal limits. They gave them 1,000 milligrams per day, or placebo.

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* Kresge 502 Cart: And

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* Kresge 502 Cart: now the in what I'm showing here is

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* Kresge 502 Cart: the in in the Women's health initiative, like they assessed calcium and the women in the trial were already taking, but on average, 1,150 milligrams of calcium. So that's their current, like their intake, you know. And and they even reported that their diet intake even went up over the trial. So they were getting at least, let's say, like 12,

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* Kresge 502 Cart: you know, up to 1,500 milligrams of calcium. So then, in the trial they gave calcium placebo. But

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* Kresge 502 Cart: maybe they didn't see any benefit, so they said, Well, you know calcium didn't protect against colon cancer.

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* Kresge 502 Cart: But you know, maybe they were just already people in like in the range where you don't see an effect. But people were getting enough cancer. So you know. So it's almost like calcium deficiency increases risk of colon cancer. So if you do a randomized trial.

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* Kresge 502 Cart: I mean there could be ethic. I'm not saying necessarily do this ethically, but

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* Kresge 502 Cart: you would ideally do it, at least theoretically. A trial with like people were low in calcium. So then you give them calcium, and then they may actually benefit. But if they're already getting tons of calcium, they're probably not gonna benefit.

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* Kresge 502 Cart: So so that's something in nutrition that you have to think about like you don't think about that in like a drug, you know, because people are not taking a drug. You're just giving them a drug. So it's a drug versus nothing. But

1:24:51

* Kresge 502 Cart: for something like calcium. People already have a calcium intake level which can affect the trial. So if you do like, 2 trials can get different answers like one. If it's done in a low calcium population, you're stuck like the trial might see a benefit, because you're studying this. But if it's if your calcium is already high.

1:25:07

* Kresge 502 Cart: Okay, that's probably the last point I'll make this is.

1:25:35

* Kresge 502 Cart: it's a similar point, but maybe a little bit different

1:25:42

* Kresge 502 Cart: another way that you know trial can get

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* Kresge 502 Cart: a misleading. I mean, if the the answer of the trial is is technically correct, I mean, if the trial is done right. But it's like, How do you generalize the finding now in in this goes back to Peter like they suggested doing a bunch of trials and actually, what was what people really were interested in Alpha to cough, which is vitamin e

1:25:51

* Kresge 502 Cart: and beta carotene

1:26:21

* Kresge 502 Cart: which is one of the precursors for Vitamin a. But

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* Kresge 502 Cart: Alpha Tacophile and beta carotene have antioxidant properties. So they said, You know, like, Wow, maybe all this benefit of like fruits and vegetables, or a lot of it is due to beta carotene

1:26:29

* Kresge 502 Cart: vitamin a and vitamin e they're antioxidants.

1:26:42

* Kresge 502 Cart: So let's do a randomized trial where they actually, they studied both. It's a like a factorial design. So you can actually randomize. So it's it's an efficient way. You get an answer like independent answers for Beta, Carotene and Alpha to cough. Well, in the same study population.

1:26:47

* Kresge 502 Cart: You can also test, for if there's an interaction, but you can. You can view them separately, because people are randomized. So let's look at the top. So what what they did is they. They wanted a population that at high risk for lung cancer. So they went to Finland.

1:27:10

* Kresge 502 Cart: and they found a group of men that were long-term smokers. These men are the worst lifestyle

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* Kresge 502 Cart: possible, but they were like long term smokers, crappy guy everything. And you know they have high rates of lung cancer not surprising. And and so they said, Okay, let's give them vitamin e alpha taco, or Beta and Beta and see like if it's protective.

1:27:36

* Kresge 502 Cart: So the top line here shows this is the incidence of lung cancer. Once the study started. So you can actually see they're at high risk. Because

1:27:57

* Kresge 502 Cart: within about 6, you know, 7 years, about 4% are accumulated like lung cancer. So that's a very high rate. if you get a population.

1:28:06

* Kresge 502 Cart: And you know, within like 5 feet, 6 years, like 4% have lung cancer, that's extremely high.

1:28:15

* Kresge 502 Cart: Not surprising. Alpha de cough roll, and that's the incidence of lung cancer. It seems like no difference. It's almost exactly the same.

1:28:23

* Kresge 502 Cart: Alfred teferall didn't work prevent lyme cancer. This truck Beta charity

1:28:33

* Kresge 502 Cart: like, okay, Betty Carotene, you know you get that Beta Carotene and carrots are high in Beta Carotene right?

1:28:41

* Kresge 502 Cart: The men who got Beta Keratin had more lung cancer than the men who got placebo.

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* Kresge 502 Cart: So That was very surprising. This was published in the England Journal of Medicine, and

1:28:56

* Kresge 502 Cart: people took this. A lot of people said, oh, like these observational studies in nutrition get completely the wrong answer. Not only do they get like.

1:29:03

* Kresge 502 Cart: not only is Beta Carotene like, not beneficial. It's not even neutral. It's actually bad fuel. So

1:29:15

* Kresge 502 Cart: so and there was actually another study, that sort of replicated that. So it's not just a freak finding. But there's one important thing to note, though.

1:29:23

* Kresge 502 Cart: So this is the range of Beta Carotene. You measure in the blood so that this gives you a sense of the range that you see in

1:29:34

* Kresge 502 Cart: the population. So the high here would be people really like carrots and orange stuff oranges things like that. And this is the low. So people who don't eat fruits and vegetables. So so this is the dietary range.

1:29:45

* Kresge 502 Cart: They gave a really, really, really really high dose of Beta Carotene, synthetic Beta Carotene.

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* Kresge 502 Cart: which was much higher than you would ever see under the diet.

1:30:06

* Kresge 502 Cart: and in retrospect they found, like

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* Kresge 502 Cart: it was being broken down to lots of compounds that were having lots of effects that you would never see in a diet.

1:30:13

* Kresge 502 Cart: So the the actually, these men were getting so much Beta Carotene that so a lot of them actually knew that they were getting Beta Carotene set up Placebo because they, if they were wearing like, let's say, white clothes. They can see the the orange and their their clothes, because it's getting such a high dose. So so so this is kinda

1:30:22

* Kresge 502 Cart: summarizes like his, like kind of my take on that Atpc trial. So.

1:30:47

* Kresge 502 Cart: you know, fruits and vegetables associated with with some cancers. Lower risk of some cancers in case control studies, fruits and vegetables are high in antioxidants.

1:30:54

* Kresge 502 Cart: in vitro antioxidants to reduce effects of free radicals, that damage DNA which treated cancer, Beta Carotene and Alpha Cartherol, Antioxidants there were actually just.

1:31:06

* Kresge 502 Cart: but were really interested at the time, you know, because people were just learning about vitamin a and vitamin e, so there could be thousands of compounds and fruits and vegetables, but they focused on these 2,

1:31:20

* Kresge 502 Cart: and they gave very high doses for men who were very high risk for lung cancer, short term smokers, I mean long term smokers, and they tested whether this could lower their lung cancer risk in 3 to 5 years. So so this kind of just

1:31:32

* Kresge 502 Cart: like

1:31:50

* Kresge 502 Cart: I word it this way, like the study question, the Atbc study is. I mean. This might be like what was the intended study question is, does having a diet moderately high compared to very low in fruits and vegetables that are rich invaded Carotene. Lower luck, cancer risk over the life course.

1:31:51

* Kresge 502 Cart: But what they may have studied is, does a dose of synthetic Beta Carotene 10 to 20 times higher than the natural diets and extremely heavy lifelong smokers. A lot of these men already have these advanced free cancerous lesions more or lung cancer risk with 5 years. So so just look at these. You could do it later. Look at these 2 questions

1:32:13

* Kresge 502 Cart: and see like, are they really the same question? The trial may have asked an interesting question, but has it really addressed the top question in terms of value?

1:32:36

* Kresge 502 Cart: Sorry. I think we're 2 min over. So

1:32:50

* Kresge 502 Cart: there are any questions II mean, feel free to leave, but happy to have questions, otherwise we'll continue Thursday.

4.

* That are looking for other people are suffocial cancer and ovarian cancer. Both of which are fascinating cancers.

1:01

* I mean, all of the cancers that we listed are really interesting in terms of the epidemiology.

1:08

* So, no, no, I saw ajial in the variant. Yeah. Okay. I'm sorry.

1:10

* I think there's about 5 students who haven't yet signed up yet. Yep, and on canvas, you should be able to see your group full lock after today after we put people in a, you didn't sign up death.

1:23

* And then there is a function on canvas where you should be able to just message my group that you're in, usually on campus.

1:40

* Oh, and then this is a last in a reminder next Tuesday, February sixth, your first assignment is huge.

1:48

* Yes. Any questions being before we start the trivia? Okay, great. So our question today is, you know, oftentimes when we do, you know, oftentimes when we do, studies, particularly when we're trying to get an early life exposures, you don't have, studies, particularly when we're trying to get at early life

2:00

* exposures, you don't have direct measures. And so we're often trying to use proxies to get at those exposures.

2:21

* So there's been some hypotheses in the literature around the role of sex halo, things like estrogen and androgens.

2:27

* So this question is in cancer epidemiology studies, which of the following have been used as proxies for greater exposure to androgens like testosterone in utero.

2:35

* Is it a exposure to DES during pregnancy. B, is it male pattern baldness? C is it the ratio of your second finger to your fourth picker or D is a higher birth weight.

2:48

* So which of these? Do you think is a proxy for greater exposure to androgen such as testosterone during, while you're a neuter.

3:00

* So not for the mom, but the actual. The infant and looking at future cancer risk. So how do we?

3:09

* Not the touch. Sorry. Oh, touch panel required. Oh, I don't know.

3:26

* I don't see it here.

3:34

* Hmm. If you turn around, I don't know if you can capture the one that's just behind you or just go to the website and pull up, Laurel, L, 900, and, 66.

3:37

* So yeah, because I don't see it right here.

3:46

* It's a little required. Sure.

3:53

* Hmm.

4:02

* Okay.

4:06

* Okay. See if I do it. All right, we'll give it just 10 more seconds to respond, Ted, 8 7.

4:11

* 6, 5. 4 3 to

4:42

* Okay, let's see. And then, go to responses. Great, so, so interesting, levels of responses.

4:56

* So, looks like the majority of students thought that exposure to DES during pregnancy and this was given to present many decades ago to prevent complications during pregnancy.

5:07

* Also, there were some answers for the other ones as well. Actually, interesting DES exposure has been linked to more rare cancers in the offspring, including vaginal cancers.

5:20

* There's also a suggestion of an increase in breast cancer, but it's actually attributed to higher exposure to estrogens rather than testosterone anderds.

5:27

* Actually, interestingly, the correct answer is the second to fourth digit. You need this. Yeah, if it's really interesting, I'm not exactly sure why it is.

5:42

* But, that ratio is determined fairly early in life and it's very strongly determined by the amount of, and, very early during pregnancy.

5:51

* And so it's interesting you see a lot of variability between men and women and also across the world you'll see a lot of variability.

6:05

* So my ratio, I mean I don't know if this is HIPAA or not? You're second before, meaning I had much lower exposure to androgens and higher exposure to estrogen.

6:15

* So it's an interesting ticket. My birthday, surprisingly actually is associated with lower levels of testosterone that thought to be higher levels of estrogen during pregnancy.

6:22

* OK. Why don't I know how to do this? Oh, sorry. Yeah.

6:34

* Okay. Okay.

7:25

* Okay. Okay. Got a call, Mike. So first question, speak loudly.

7:32

* I can't hear. Okay, so yeah, so we talked the Tuesday, right? So I covered the first 2 like, background, a wide diet, okay, so, yeah, so we talked, Tuesday, right?

7:44

* So I covered the first 2, like, I covered the first 2, like, background, so, yeah, so we talked, Tuesday, right?

8:04

* So I covered the first 2, like, background, a wide diet, maybe important for cancer, and then we discussed a bit about observational randomized trials.

8:12

* So, I'm going to finish these last 2 topics and then get into, like body weight and physical activity.

8:19

* So I'm not going to give, like this is more to help you like assess dietary nutritional studies throughout the course, like for specific topics, you like assess dietary, nutritional studies throughout the course, like for specific topics, you'll get more specific knowledge of the nutrition cancer association, particularly for example in colon cancer, where there's a lot of dietary association.

8:23

* So I won't get into a lot of specifics, but be kind of broad. So a big question, different ways to measure diet in large studies.

8:40

* Now, the best way to to measure diet in small studies like if they're doing a study like without a hundred people or something like that, you can have dietary records where people are instructed and they measure.

9:01

* Whatever they eat, they record everything. Sometimes they even have like a scale. And they're supposed to be very dedicated.

9:16

* And of course you can't do this for a year, but you can do it like for a week or something in multiple weeks.

9:23

* I'll talk a little bit about that. Then most of the data are food frequency questionnaires.

9:26

* For better or worse you know they get criticized sometimes but that's where almost all of the available data are 24 h recalls are sometimes used.

9:36

* Now, bial markers are not you know, there are few biomarkers that tell you exactly what somebody is eating, but they're like indirect.

9:43

* So for example, if you eat lots of fruits and vegetables, your blood beta carotene levels will be highs.

9:57

* We talked a little bit about beta carotene last time. And then I just, you know, they're like maybe this is more for the future, like O Mix.

10:04

* Things like metabolomics where you measure lots of metabolites and again these don't really tell you exactly what someone is eating, but they might be useful in indicating what the effects of diet.

10:13

* And then there are things like iPhone apps, like, you know, you take a photo of your mail and then it somehow, it's measured.

10:26

* You know, those could be useful but they're not perfect like for example they won't distinguish between a diet coke and sugar sweetened beverage, which would be something very important, like to miss the misclassified, just because visually you can't tell the part.

10:30

* There any questions or?

10:51

* Okay, now. It's also like, you may recall, The last time we talked about, you know, different ways to conceptualize diet.

10:55

* It's not like a simple exposure. Like, you know, number of cigarettes per day. Their complexities with tobacco too, but it's a fairly, you know, one dimensional, how many cigarettes you smoke a day.

11:07

* Diet, you can look at it in a lot of different ways. And the later I'll talk about like an energy balance just like if you're eating too much more than you're spending.

11:21

* And there's no really good dietary assessment to that. I mean you would have to have like almost a perfect measure of caloric intake.

11:29

* And almost a perfect measure of energy expenditure. So the balance in minus out and neither one of those are really that feasible in epidemiologic studies that you can do studies like a small metabolic war type of studies but they're not feasible.

11:43

* In fact, given in small metabolic ward studies, there's a fair amount of measurement error.

12:05

* And you know, like if someone Like, you know, you have to measure. Things almost perfectly to get energy balance.

12:06

* So like if you, 100 calorie a day difference over like many years. What will increase your body weight, maybe a few kilograms.

12:17

* So you need always a perfect measure, which is really not feasible. Now for some of these aspects of diet other than energy balance, like FFQ, 50 questionnaires are currently the best, being the best ways for micronutrients, the best ways.

12:23

* For micronutrients, you have biomarkers, like you can measure blood beta carotene, which again doesn't tell you exactly how much.

12:47

* Person beta carotene they consume because it also is affected by absorption and breakdown in the blood.

12:54

* You know, there are lots of factors, but it gives you a pretty good indicator like on average people who eat more.

13:02

* Beta carotene will have higher blood levels. So they can be useful. They're more objective markers.

13:09

* And I also mentioned RCTs because you can actually feasibly do RCTs for this.

13:16

* And then things like carcinogens and contaminants. I think a good example, carcinogen is that there's something this is something Laura Live, studies called the chromeide.

13:23

* Which you get like if you like let's say toast or You cook. Brad, I think it's mainly st and there.

13:35

* They're putative carcinogens and like, and so you can measure them like in red blood cells because they buy to red blood cells.

13:46

* A little bit like he, I think, heema Global, A. OneC concept like for glucose measuring diabetics.

13:54

* So they're getting good studies done by Lori and others that, for example, shown reassuringly that they're not at least associated with cancer risk, which is good for me because 2 big sources are like toast and coffee, which that would kill my breakfast.

14:01

* Probably most of you have seen, food frequency questionnaire, I just show one here.

14:29

* I think this is front of one of our cohorts. And so there's an item like, I think the current one has about 140 items.

14:37

* And, you know, so for example, skim or low fat milk, 8 ounce glass and there's 9 categories.

14:46

* And your report like over the past year, so this is your consumption. Sometimes people say, well, this is your consumption.

14:51

* Sometimes people say, well, how could you remember over the past year. Sometimes people say, well, how could you remember over the past year.

15:05

* Sometimes people say, well, how could you remember over the past year? But actually, the longer-term memory is sometimes even better than short-term memory, sometimes even better than short-term memory is sometimes even better than short-term memory is sometimes even better than short term memory is sometimes even better than short term because because you might have a sense of like, oh yeah, I have like the longer term memories, sometimes even better than short

15:06

* term because you might have a sense of like, oh, yeah, I have like chicken pretty consistently 2 times a week.

15:20

* You know, that's I guess we did have the last night yet, but I just happened. But I did like last Friday. I don't know what it meant.

15:25

* So the long-term memories, and actually that's what you really want for for cancer studies because remember we want long-term dietary.

15:29

* And take. An important question is the accuracy of how accurate are these. I'm sorry that thing.

15:45

* So, how do you assess it? Like, so how do you assess it? Like, actually, Dr.

15:49

* Willett, who's in department, and nutrition here. Who is my advisor.

16:10

* Like, led some of the studies and, you know, he did a lot to show that nutrition can be assessed in epilogic studies.

16:17

* And one of the first studies, and now they've been multiple studies like this, is this is like in a nurse's health study and what they did is they sent the questionnaires like, it's 100,000 women.

16:29

* So FFQs, but then they wanted to know how good the data was. So, and a sample of 173 participants that happened to be in Boston just for feasibility, assuming participants from Boston, their representative.

16:45

* The whole country in terms of so And these women, they did, they tuck it, they did a food frequency questionnaire, say June, the nineteenth, 80 and the second one in June, 1,981, then did 4 one week diet records.

17:01

* And remember, diet records are considered the gold standard. So, you know, the 4 weeks is a pretty, you know, that gives you a pretty good long-term estimate.

17:21

* What a person would be consuming, like, over a year or so on average. And then like you average them.

17:34

* These are the correlations between some of the items. So a perfect correlation would be 1.0.

17:41

* On average, you know, It's, the average about point 6 4.

17:52

* And so it's not like They're not perfect and of course the diet records aren't really perfect either so there could be some measurement error in guide directly.

17:56

* So it's a good concept to keep in mind. Like sometimes when people say like let's say you're assessing something, sometimes when people say, let's say you're assessing something compared to a goal standard.

18:12

* The goal standard sometimes is not perfect and that's particularly true in some of those studies with energy balance.

18:23

* There's actually a lot of measurement error in the lab of getting like the exact energy of expenditure for example and then like you correlate your surrogate with that and your surrogate may not you know the correlation may be over than you expect but some of that could be error from your gold standard.

18:29

* But in any case, These are, you know, these are the kind of correlations to keep in mind that when you're looking at diet and cancer, like most of the studies have correlations and it varies by You know, nutrient, some are better than others in Lodocanas that here are pretty close.

18:51

* Like protein is a little bit lower. Than the others. And the reason for that, is actually what correlations, your range of consumption, it also.

19:11

* Contribute to your correlation coefficient. So protein is more restricted in the population. You don't have people having like 90% of the calories from a protein or 5%.

19:27

* They're all like, 90% of the calories from a protein or 5%. They're all like around, you know, like 15 to 20% that range.

19:39

* So if you have a restricted rate, you have a lower correlation. So in a sense it's not so much that the absolute measure is worse than the others.

19:43

* It's actually that you have less variation. Population. I should know this answer, but depending on the time of the year, the season of the year, was there any variability or these estimates kind of consistent?

19:52

* By season. I'm just thinking you might eat more fresh foods and vegetables in the summer. Yeah, it's a good question.

20:10

* I don't know if that's been looked at specifically, but the way the questionnaire is worded, it's been looked at specifically, but the way the questionnaire is worded, what you're supposed to do is integrate in your mind like the year so like so for example like if you eat a lot of peaches in the summer but not in other months like that.

20:14

* You know. You're supposed to take that into account. So, which is could be a little bit difficult.

20:38

* So that probably does add noise. And but it would be interesting to see like for example people who responded in the summer versus people responded in the winter.

20:46

* Like, you might get a bias where people respond this summer reporting more fruits or like let's say peaches or something like that.

20:56

* Yes. Good question. Does anybody have any thoughts on that? So, yeah, I mean, that's a good rule of thumb.

21:07

* Yeah, I mean, that's that's a good rule of thumb I mean if there's no I mean that's a good rule of thumb I mean if there is no I mean like point for me like point 2 is definitely too low.

21:26

* I mean, there is no, I mean, like, point for me, like point 2 is definitely too low.

21:36

* It's very low. Point 8 would be. You'll be very happy if you get that in theology for tradition.

21:38

* Personally, I'd say like below point 5 would be problematic. The other thing to keep in mind is one of the advantages of the nurses.

21:50

* And health professional studies, which is pretty unique, is that there are multiple measures like every 4 years. So participants fill out a questionnaire.

22:00

* So some of reports have like 8 or 9 questionnaires over their life. So that kind of, you tend to get Probably better information like more people because you average over a long time a lot of studies have one questionnaire for somebody's lifetime so like age 50 they start to study they fill out their questionnaire and then they could be followed for 30 years.

22:08

* And so, you know, in top of the measurement error from the questionnaire itself, Then, you know, does the error from having one year or assessment followed for 30 years?

22:38

* But I'd say about like, you know, point 5 is the rule of thumb. I like to see like I get happy when it's about, 0 point 5 is the rule of thumb.

22:48

* I like to see, I get happy when it's like, 0 point 7. But point 6 is, is sort of acceptable.

22:59

* There are also, like, Molin, and every department like she and Donna Spiegelman who was here have done a lot of like formal measurement error correct.

23:00

* So you have the data from the validation study. Which you can kind of use to, adjust your findings in your studies because of the measurement error.

23:20

* So things that have a lot of measurement error. Like you kind of take that into account. Like, so for example, if you see.

23:32

* Like let's say a relative risk of 1.5. But you know how much measurement error there was in that estimate that could bump it out to like 2.0.

23:40

* So conceptually you say, well, if we had a perfect measure. We see even a much stronger relative list than one.

23:49

* People sometimes don't like that, but that's, you know, one way that it's dealt with.

24:01

* Another way, sorry, the slides a little, complicated, but, Yes, so let's see.

24:09

* You You have like, what this show, let's just focus on foli here. There are different biomarkers here.

24:16

* So this is another validation study that was done more recently in the men's validation study. This is like the health professional study.

24:27

* So what they did is they had like different measurements on these men about 626 men a single That's a 24 h recall, 24.

24:39

* A 4 24 h calls. An FFQ for food for can see questionnaire.

24:51

* And then this one is average, so they're 2 for averages. And then a single and.

25:05

* 2 weeks of diet records. So, so they have all these measures and then they have a bayer mark.

25:13

* So full aid is measured in the blood. And again, you know, as I mentioned, your dietary foliage should be correlated with your blood flow, but it won't be like 1.0 because you know, you people absorb falling differently and gets broken down.

25:17

* But, you know, there should be a correlation if you have high flow. So, so these are the correlations like so for an average 7 day diet.

25:36

* Correct. So this is, you can think of this as a gold standard. The correlation, you know, it's about point 7 here.

25:49

* And then the second one is single seventh day diet director. So, so this actually, this is nice because it sort of gives you a sense of like if you have 1 7 day diet directed it's actually not much worse than having to.

25:59

* You know, correlation is a little bit lower. The higher the correlation, to zoom like the better the higher the correlation to zoom like the better the measurement but it's not like the better the measurement but it's not like a big increment.

26:16

* But it's not like a big increment. But it's not like a big increment.

26:26

* And this is the, food frequency process, 2 food flips. So this is like showing that at least for falling food fields.

26:27

* So this is like showing that at least for falling food frequency questionnaire is really not much worse than a food frequency questionnaire is really not much worse than a one day diet record, or one week directed.

26:36

* And, you know, not that much

26:47

* 2 weeks of diet records which you know would be like there actually isn't any large study that has 2 weeks of diet records, epidemiologic studies.

26:50

* Like some people have argued that while you can't believe in full frequency questionnaires, you know.

27:02

* You should do studies that like a multiple week diet directors. And yeah, that might be better, but it's not, you know, at least for some things it's not much better.

27:08

* Now what's interesting is you see a bigger difference. For sodium where the diet records are better.

27:18

* Than the food frequency question for Sodium. And the reason for that is that, sodium varies a lot in foods like, you know, things like folate or, you know, protein, potassium, someone eats like, you know, serving a red meat.

27:25

* Those items should actually be pretty consistent. Like, you know, particularly something like potassium. You know, it'll be pretty much the same in all kinds of meats.

27:45

* But sodium depends on processed foods and some add a lot of sodium. Some, you know, add much less.

27:55

* So. So like you do like the FFQ does miss some of the specificity. In some cases, but for some broad items like potassium or foli, it actually does pretty well.

28:03

* Okay, so, yeah, sorry. That we would want to use a full frequency questionnaire as close to a diagram.

28:19

* Yes, it's much, much, much less expensive. Yeah, yeah. Food frequency questionnaire, food frequency questionnaire, is, like, you know, It's almost like pennies.

28:29

* I mean, when the study started like in 1,980, I know this sounds kind of like low, low tech now, but one of the big, improvements was like optical scanners like you fill in the little bubbles.

28:43

* He's gonna help us with our touch panel required, sorry. Hope it's worth.

29:02

* Okay. Oh, wow, what did you do? The room was just in video conference mode, which our users, so likely the people for you.

29:15

* That was fast. I was worried it's gonna be like 40 min. I was worried it's going to be like 40 min.

29:30

* So for example, I'm sorry, your question, yeah, the frequency question. Yeah, they're like the diet record, like so for example, and the food for, yeah, instead of optical scanners, you know, which.

29:45

* Basically, it's like you fill in the little bubbles like that. I mean, this is like, 1980.

29:56

* Wow, we can send this out to 100,000 people. That made the study very feasible to do in large numbers, even though it was all done by the mail.

30:00

* Use like the internet like that. But like diet records, you need training from a dietician. So it would be like, mag, like even 170, women that studies, that that part of the study was very expensive.

30:10

* Appear to the like 100,000. For you. So it's exactly it's it's just costs and feasibility.

30:27

* Well I mean that that and also participants like, you know, should take you, you know, I don't know, like, 20 min, maybe like half hour if you're very careful.

30:37

* Diet records have been matching like every meal you're bringing a little scale like so yeah there's a also the participant though And then it's also like once.

30:50

* Like the FFQ like you make assumptions like this item has like this much potassium with the diet records is a lot more variability in the foods that are accessible, which is an advantage in a way, but then you have to have a dietician look through all the items like somebody's eating something and they typical like that.

31:09

* So there's a trade-off, you know, but I think like this kind of study, it gives you an idea like, well, is it worth like?

31:31

* Yeah, it would be great to do, even like 4 one week diet records during the study.

31:42

* Or like why not like one year diet, right? It's people every day they record their data.

31:48

* But there's always a trade-off. So how much worse is the FFQ?

31:55

* The FFQ is definitely, you know, not as good, but it's, you know, for a lot of nutrients, it's not much worse.

32:00

* Okay. I'm just going to quickly go, and again, we'll see examples in in the specific cancer as we discuss like the nutrition cancer associations.

32:11

* But I just wanted to give a very broad overview about assessment of evidence and this actually, you know, I mean, this is not much different from what you have, you know, hopefully you're getting this in your courses like in epidemiology like how to interpret evidence broadly from lots of studies.

32:23

* And I just used the WCRF the ICR, that are, you know, they have a, their, their existence is, is to assess nutrition and the cancer.

32:43

* And so I was on like their panel for about 10 years. So the way they assess the data, so they look at all the way they assess the data so they look at all the like just about any question like you know coffee and colon cancer you know sodium and breast cancer, anything that there's data out there.

32:50

* And so they do like meta-analyses, things like that. So they, so the conclusion, so based on the methodologic, you know, rigor consistency across studies and, you know, bigger consistency across studies and I underlying prospective data.

33:22

* I'll talk a little bit about that because there's a lot of case control studies and I underlying prospective data.

33:40

* I'll talk a little bit about that because there's a lot of case control studies too. There's also experts in the group that help and integrate epidemiologic findings with the like mechanistic data, animal studies, biologic plausibility.

33:43

* And then like the, at the end of the days that these experts sit around and come up with convincing probable or limited data or evidence.

33:58

* I'm not sure if this will be keep going in the future, but they had like 3 big reports.

34:14

* I was just involved in the last one. About every 10 years because things change all the time, you know, so now, talk about this briefly, but Laurel, I already mentioned.

34:20

* Like case control studies and cohort studies. And, she mentioned that study that indicated there was recall bias.

34:35

* I'd already showed this slide last week. Just Just to remind you that in 1990, there was evidence from case control studies pretty consistently that saturated fat and take was evidence from case control studies pretty consistently that saturated fat and tank is associated with a higher risk of dress cancer.

34:39

* And then, in, The. These are like.

35:06

* From a told analysis of cohort studies. I was published the 1,996 New England Journal of Medicine.

35:15

* This is like from, this included the nurse's health study but also other studies. And you can see very, very now a finding for fat and percent energy for fat.

35:25

* Going from a pretty wide range of less than 20% greater than 45%. So the fat composition of the diet from prospective studies were very different from the case control studies which tended to show an association.

35:38

* And now that they're even like, I think this number is probably like 10 times larger.

35:56

* There's like, it's completely flat. And you know, and at some level, even like with 50,000 cases let's say you know even if there is like 50,000 cases let's say even if there is like measurement error even if the correlation is like point 5 like what you know fat and take measured versus real fatigue, should probably see something, a hint of something, 50,000, like you see

36:01

* nothing. So the cohort study is pretty. Consistently show no association with the fat. And why do you think is the main reason for the difference?

36:24

* I mean, there are several differences between these 2 designs and I assisted later through each one of them.

36:40

* These studies, what was the main? Yeah, I think there's 2 potential, well, some people have argued and I think this was a reasonable, well, some people have argued, and I think this was a reasonable argument like maybe 20 years ago, but I don't think it is anymore, that like some of the cohort studies had one measure.

36:43

* And then they had the long term follow-up like 2030 years. So, so some people who were like pro stat hypothesis.

37:09

* They argue like, well, the cohort studies have more measurement error because because they have a lock follow, whereas the case control studies.

37:18

* Ask about recent diet. And maybe recent diet is more important. Now that would be a, you know, at least a plausible argument.

37:26

* But there's a, like you can look at the subset of cohort studies that have like 5 years of follow up, short enough follow ups like so it would be similar to case control studies and they're pretty null too.

37:36

* The other thing is that like Like some would argue, well, the methodology in the case control studies is better, like the dye assessment is better.

37:50

* But that's not really true. I mean, they use similar, it's not like the case control studies have a perfect measure.

38:00

* So there's a similar measurement error. The 2, you know, plausible reasons are recall bias, the 2, you know, plausible reasons are recall bias, and selection bias.

38:03

* In fact, I'll, this is, These are. We actually did this about 5 years ago we just looked at summary of adherence to healthy dietary patterns and risk of cancer.

38:20

* I'll explain a little bit what we mean by healthy dietary patterns, but just ignore that for now.

38:39

* But, so, so these are, summary of the literature at the time and you can see for a lot of cancers.

38:44

* There's for case control studies you see except for prostate you see an inverse association so good diet lower risk and for prospect of studies.

38:52

* Not much there, you know, a little bit for colon cancer, colorectal, that is a significant, but it's much weaker.

39:06

* It's like, 0 point 8 9 versus point 4 8. And this is looking at like high versus low one tile like that for brass, you know, a little bit.

39:09

* So, you know, if you look at the case control studies, you conclude, while a healthy diet dramatically reduces your risk for, you know, most cancers except prostate.

39:24

* Whereas the cohort studies show, and you know, it's not that promising, a little bit there for Colin and Brest, you know, so like I think one of the biggest issues in in recent I guess I would say decades now.

39:28

* Is that in case control studies, like what people do like to get the cases are relatively easy to identify.

39:51

* And then you have to get controls. And controls like they were done by like random digit dialing because you want to get, so for example if you're doing a case control study in Boston so you have all of the you know colon cancer is in Boston or identified then you want like a random sample of the Boston population.

40:03

* So what they would do is they would get like like if anybody had a phone their brand that you can randomly get call okay so you can think like first of all not everybody has phones and then not everybody answers.

40:27

* And then the people who answer are going to be. Likely bias to people with a good diet. Like if you have, you know, if you know even subconsciously that you have this crappy diet, I don't, I don't think I want to do this study, but if you, you know, really health conscious and you're like, go, you live at Whole Foods like that.

40:45

* You might like, you know, oh yeah, I'll participate in this study. So you can actually show like response rates could be 30, 40%.

41:04

* So I think there's a lot of participate in this study. So you can actually show like response rates could be 30, 40%.

41:15

* So I think there's a lot of, so I actually think the selection bias is probably even more important than the recall bias.

41:20

* So, but it is quite amazing how many, it's actually a little hard for me to explain why case control studies like so often get a protective or if they're looking at something, bad, like, you know, perceived to be bad, they have a positive association.

41:21

* But it's pretty consistent as the prospect of studies are pretty, So I guess conservatively will go with the prospect of studies.

41:37

* There's still some people who will argue the case control studies get the right answer. Okay, so this just, you know, this isn't an important, like you don't have to memorize this or anything, but this just shows that how the WCRF.

41:48

* You know how you know they make recommendations and and the criteria basically the hills you've probably got Bradford Hill criteria like you know.

42:14

* Like all of these with. Would contribute to something being like strong evidence. There are not many things that actually get strong convincing evidence, but there are some items that we'll see that get like probable evidence.

42:26

* And they would still be considered probable, still pretty strong evidence, which that they could actually make recommendations. But, just as a point.

42:44

* They first review the science. Come up with this list. And then the recommendations are made later because like recommendations might be, you know, like for example, like what if there's something that seems pretty consistent that's good for cancer but that's let's say bad for cardiovascular disease so you don't you don't want to just make recommendations based on the findings.

42:57

* The For now, this is just a summary of. The findings and a lot of these. Will be talked about later in the course, but this is a list of what the WCR FX here came up with as related to cancer with strong evidence like probable or convincing and at this, now, like, the second in a few minutes, I'll talk about energy balance, which seems to be

43:25

* the most important. And I'm also excluding alcohol, which is part of diet in a way, but that's a different topic.

44:00

* But, this is the percent of cancers that are attributed to all the potentially and you can see that they add up to about 5% so so in other words if people did well in all of these, lower sugar sweetened barriages, lower red meat for example.

44:12

* They, you would prevent about 5% of the total cancer. Now, Interestingly, this is dominated by colon cancer.

44:36

* So almost like for all at least. From what we know from what they list as probable or convincing evidence.

44:47

* Most of the prevention from diet would be for colon cancer. So out of the 5% like I think you would have like 80% of these would be colon cancer.

44:51

* Which is interesting. So, so there is a, you know, it's not like not nothing, but it's not like traumatic.

45:10

* But remember that this is independent. So this is like just selecting specific items and trying to elect them to cancer.

45:14

* Now, I think in the future and actually WCRF, I'm actually working on a project with them.

45:30

* They're a lot more interested in dietary patterns. They're a lot more interested in dietary patterns.

45:31

* They're a lot more interested in dietary patterns now. Dietary pattern rather than looking at a single item.

45:39

* It's just a definition from the US guide theory guidelines. Dactory patterns are a combination of foods and beverages that constitute an individual's complete dietary intake over time.

45:46

* This may be a description of a customer way of eating or a description of a combination of foods recommended for consumption.

46:00

* There are some advantages, from looking at a dietary pattern than just the specific item like I'm just going to focus on red meat.

46:09

* But, you know, I just make a list here of argument why conceptually it's better to look at it.

46:21

* So for example, the whole looking at the whole diet with, you know, like any single item might have a small effect, but if you look at, any single item might have a small effect, but if you look at, 20 small effects, they might add up to something substantial.

46:30

* It's also, you know, in some ways it reduces like the confounding and just as an example.

46:46

* So when you look at a dietary pattern, like let's say for example, you're looking at the effects of a vegan diet.

46:56

* You're not like necessarily saying that they're like like anything specific like, oh, it's the carrots that that's important.

47:05

* In fact, it may also be that like a vegan diet by, you know, definition excludes animal products.

47:14

* So if you see like a vegan diet is beneficial. You just say, okay, we see a vegan diet is beneficial.

47:20

* But it's not like you have to make a statement like, oh, like red meat is bad or cheese is bad or like red meat is bad or cheese is bad or carrots are good you're just talking about the whole guy. It's bad or, carrots are good. You're just talking about the whole diet.

47:23

* It's a more general statement. It's a more general statement. It's probably more conservative than trying to find a whole diet. It's a more general statement.

47:42

* It's probably more conservative than trying to find a single factor. It's probably more conservative than trying to find a single factor.

47:45

* And it's potentially more conservative than trying to find a single factor. And it's potentially more beneficial.

47:48

* There are different ways, so what do you mean by dietary pattern? I'm gonna talk a little bit late, I'll mention.

47:52

* I hypothesis oriented, but most of them are based on scores on prior knowledge. So this is just to give you an example.

47:59

* There is something called alternative healthy eating index scoring. I mean, this is probably more give for cardiovascular disease, but, Like you get points like basically there are like good things, presumably good things like vegetables and fruits, whole grains, where you get like points by eating more, then you get negative points by eating or drinking sugar sweetened beverages or like processed meats.

48:09

* trans fad, which you know is not an issue now, a sodium like so it's basically kind of a score but it's based on the consensus of what's good in one's bad.

48:43

* Which could change over time.

48:56

* And, we actually did a validation study. Shouldn't say I mean I wasn't directly involved in this but the and 2 weeks of diet records and FFT frequency. They're pretty good correlation.

48:59

* So for frequency questionnaire does pretty good at. Picking up a dietary pattern, which to me intuitively kind of makes sense because, you know, like someone might argue like, well, how could a full frequency question here be tell you the precise amount of beta carotene someone's eating or something.

49:10

* That's a little bit harder to get, but if you're talking about a whole dietary pattern, people tend, you know, there's some people tend to eat a lot of healthy foods and some people less so.

49:31

* And so I think you, you know, does at least to me intuitively, I think it makes sense that you are likely to pick up, you have good information, diet.

49:49

* So, so you're getting like good general information. Of course, you're losing some specificity over what I specific item might be.

50:00

* The interesting thing is like we're doing this summary for the world's cancer research fund, summarizing dietary patterns and summarizing dietary patterns in colorectal cancer research fund summarizing dietary patterns in colorectal cancer research fund, summarizing dietary patterns in colorectal cancer.

50:09

* Where this is an official, I mean, we do, in, in, I can tell you even though I shouldn't you know it's not like published yet or anything but some of the dietary patterns do seem robustly associated with total answer.

50:18

* But what's interesting is you see there's like a lot of dietary patterns. And so it becomes like, you know, what is the advantage of dietary patterns?

50:37

* Is like you're integrating information, dietary patterns is like you're integrating information, but I'm almost thinking now it's becoming like you're integrating information but I'm almost thinking now it's becoming like there's too many.

50:46

* But I'm almost thinking now it's becoming like there are too many. Some of them you might be like, they're too many.

50:54

* Some of them you might be afraid of like the dashed diet, some of them you might be like, you've heard of like the.

50:56

* So some of them you might be like, you've heard of like the dash diet, the, healthy eating index, the, Mediterranean diet should be somewhere.

51:01

* Yeah, it's the first one, Mediterranean. And then there's some, like, you know, there's Danish dietary guidelines.

51:02

* So anyway, I'll talk a little bit about more about those later, but I want to spend, you know, make sure I have some time to get into obesity.

51:08

* But I just want to spend, you know, make sure I have some time to get into obesity.

51:23

* So this is just a quick summary of what I've talked about so far, I have some time to get into obesity.

51:26

* So this is just a quick summary of what I've talked about so far, including last week. So our randomized trials would be ideal, but.

51:29

* There is limited utility for most questions for nutrition and cancer. Case control studies seem to be prom to recall selection bias, making cohorts the most feasible.

51:34

* That's the most feasible. And you know correlations we discussed about roughly about point 5 to point 7 for most things.

51:47

* There's some things that maybe are not measured well. Established factors outside of energy balance contribution are red process needs fibre whole grains, dairy, calcium, fruits, vegetables.

51:56

* They contribute to about 5% of total cancer and about 40% of colon cancer. And so the next part.

52:09

* Is going to be obesity and fiscal activity, which we'll see is probably more important.

52:16

* Now, you know, how is adiposity measured? So does anybody like mention a way that we measure or received?

52:28

* You can look at the next slide, don't she? Wait, yeah, that's a good way.

52:37

* Oh, oh yeah. Yeah, the bio impedance that they shoot some like electricity and then like if you have more fad I think like you have the bio impedance that they shoot some like electricity.

52:48

* And then like if you have more fad I think like you have the conduction is lower. Salesforce.

53:05

* Oh, like calipers like those. Yeah, yeah, that's right. That would be right.

53:16

* That's right. Any others? Right here. Oh, sorry.

53:17

* Yeah. Yeah, BBBB is always like controversial, but yeah, but I mean it does like, it's actually not as bad as people think at least for some cases we'll see. Right. And then there's, yeah, I have to have a list here.

53:29

* So I think it's actually not as bad as people think, at least for some cases we'll see actually not as bad as people think, at least for some cases, we'll see. Right, and then there's, yeah, I have to have a list here.

53:47

* So most of if someone gained like, you know, 20 pounds like from age 30 to 50 I must they suddenly became like a body builder that's mostly fat you know well it's not I mean it's actually even when you came wait you also do gain like some muscle but it's it's predominantly like fat.

53:57

* So that's kind of an indirect way. And then, I'm gonna talk a bit about visceral, and a little bit about her patic fat, which is, you know, like you can't get that visceral and a little bit of autopatic fat, which is, you can't get that from what a simple measure you need.

54:21

* The scanning like CT scans or depths.

54:36

* Now, this is the punchline for just using BMI, which is not perfect, but you know, it's a crude measure of fat.

54:41

* They're 13 cancers that have been established as causally related to be a higher BMI.

54:49

* And now i think lower live mentioned which will get talked in the breast cancer that breast cancer is a little bit like, you know, early life BMI is actually associated to.

55:03

* Protective effectiveness cancer. So high B and I, but in post metopausal women like weight gain, for example, it's definitely a risk factor.

55:18

* And you can see that there's a variation in like the magnitude like 4, and so these are for 5 kg meter squared increment based on a container.

55:27

* So for at the metro and for Admiral Carson on the soft is a pretty strong association.

55:35

* And but for others it's, you know, a liver are pretty strong. Some are pretty weak.

55:45

* So like, you know, like for a veryvarian cancer, BMI, I mean excess body weight, you know, if you had to give like a percent like, you know, it might account for about 5, maybe 10% of where in Kansas.

55:51

* So it's not like the smoking in lung cancer, but it is a contributing factor. But when you look at like that it's dirty cancers, they do add up.

56:08

* So if you're looking at total cancer, it's actually pretty, it's not trivial.

56:13

* The other important thing is I'm sure, you know, everybody's aware of that.

56:24

* Increasing . in in younger population, young adults, and for a Monday obesity related cancers.

56:30

* So I, here I have 12, okay, 13, but guess. You know, I, I won't get into a little detail, but let's say they have 12 here.

56:45

* 9, among young adults like young onset, colon cancer. You have, like 9 out of the 12 are increasing.

56:53

* In association with increasing adiposity. Of course, this does not prove that it's the adipocity that's increasing the risk, but it is, It is consistent.

57:02

* It's kind of what you would forget. Yeah, young onset calling kids. It's by definition.

57:24

* So can't any cancer like before the age 50 like there's been a lot in the news recently about colorectal cancer like that so This is one cancer that I cannot get.

57:33

* But, so this is a worldwide that this is how many cancers are attributable to excess body weight.

57:40

* And you can see from men the big ones are liver colorectal kidney. For women it's breast and a metral colorectal in fact for in terms of cancers of cherry bolt.

58:01

* Obesity is much higher in women than in men, almost like twofold. And that's predominantly because the end of mutual cancer and breast cancer.

58:17

* Yes. Oh, it's coming up. It might even be in a probably 2 slides or so.

58:29

* So, and just just to point out that, there, there are differences by grace and ethnicity and adult obesity and now it's interesting that in Asian, this is using BMI as the standard BMI.

58:45

* You know, like above like 30 which would be the But for the agents like the standard should probably be lower because of the different body composition, which of whichel talked about a little bit.

59:09

* But anyway, there are some racial differences in obesity that probably contribute. It's not like maybe the big dominant factor, but it does contribute to some of the differences in cancer rates.

59:25

* For like potentially breast cancer. Yes. This is the mechanisms now. Okay.

59:37

* So. So I, I think they're. Broadly, there are lots of research, you know, people delving deeply into mechanisms.

59:42

* But broadly, I think there are 3 major mechanisms. And, Let's see.

59:54

* Yeah, okay, so this slide. Shows, I'll talk a little bit more about this, what I mean by cancer triad, but because diet and physical activity impact on obesity and obesity affects all of these estrogen levels.

1:00:01

* In pulse metopausal women and in men most of the estrogens are made in adipose tissue.

1:00:26

* So the more adipose tissue have. It's just, it's basically a converging of like anrogen to best proteins.

1:00:33

* You know pre menopausal women obviously it's different it's the oak area and the post menopausal women, like if you do just even a cross-sectional study.

1:00:40

* Body weight, BMI, and estrogen level. There's a linear association. So an estrogen which you'll hear about in future, like I guess there's electron breast cancer, a group that will be looking at at the mutual community.

1:00:52

* And, I don't know what specific topic you'll, but when you talk about the topic, you'll, you know, but when you talk about individual cancer, you have to at least mention, obesity, cause that's like.

1:01:10

* That's almost like smoking and blood cancer. I mean, obesity is very important. Now, and then I'm gonna talk, most of my talk will be about this middle part here, but just.

1:01:21

* By local inflammation like gallbladder cancer is related to obesity, most likely that the main reason is that obesity causes gallstones and the main risk factor for gallbladder cancer, which is rare in the US, is golf.

1:01:33

* So you have got stumps for many decades. If they cause a queue. Sentence, then the gallbladder gets removed and then you don't get involved a lot of cancer but if the stones are there asymptomatically for years.

1:01:50

* That that could cause God blood cancer. And then, I don't know, carcinoma with the oesophagus, and that's, Jail can't just another one of your topics so so acid reflux so obesity, particularly in men because it's central because it causes like the acid from the stomach to go into the lower part of the esophagus.

1:02:02

* And, and so the suffrageal, the 2 types of main types of suffix, this cancer.

1:02:30

* One is, add, no squams, which is in the upper part of the esophagus, which is due almost entirely to smoking and alcohol, you know, poor diet quality, probably continues, but smoking alcohol, the lower part, adamo carcinoma is probably continues, but smoking alcohol, the lower part, adeno carcinoma is just the part where you get the reflux.

1:02:36

* One or 2 cm right at the bottom. So the chronic They're rotation due to the acid.

1:02:56

* Now, I'm going to talk a lot about insulin and inflammation which which are related and I think these are the multiple cancers which I'll talk about.

1:03:06

* So just remember like chestrogen for these cancers, we'll talk about that later. And then these very specific mechanisms localize information for gallbladder esophagus.

1:03:20

* So like insulin, I mean most people think insulin diabetes, right? That has something to do with diabetes.

1:03:26

* What does it have to do with cancer? It's, actually insulin is a growth factor and, cod like it's, it's, if your insulin level, this is my simplistic way of thinking about it.

1:03:35

* If you if you're not eating a lot you know energy restriction. Your insulin novels will be low, right?

1:03:55

* And that's indirectly signal to the body. But you're not eating a lot.

1:04:04

* So why should you be having a lot of cellular activity, particularly in the gastrointestinal system.

1:04:11

* Log insulin reduces soft full of fluorine. And, and there's, I mean, I'll talk more about the epidemiologic studies.

1:04:19

* There's even like, Like, Gillian randomization, which I. People familiar with that, 1 billion.

1:04:27

* I Like, it's basically using genetic variants to test the causal hypothesis.

1:04:42

* So for example, people that have genetic variant that makes their insulin levels a way higher than average.

1:04:51

* Those variants are consistently associated with what some of these cancers, particularly colorectal cancer. So that kind of gives pretty good causal evidence.

1:04:59

* The problem like if you're studying something like insulin from epidemiology, you can measure insulin, see if it increases risk, which is fine.

1:05:04

* And it does, studies consistent, you know, show their high levels of insulin.

1:05:18

* But, you know, Islam is going to be related to a lot of things. Basically, if having too much quality waiting for since long, but I don't increase like 100 other things long, but I don't increase like a hundred other things.

1:05:24

* So it's hard to PIN it just to insulin, but I don't increase like 100 other things. So it's hard to PIN it just to insulin.

1:05:36

* This actually, Mendelian randomization studies to suggest that it's actually the insulin level that's the causal risk factor, which kind of makes sense.

1:05:39

* And I won't get into a lot of, you know, this stuff. Which I don't have a great understanding.

1:05:45

* You know, this stuff, which I don't have a great understanding either, but there's like people from a laboratory perspective.

1:05:48

* There's good evidence that insulin stimulate receptors. These are insulin and IGF one receptors that are important for metabolic signaling.

1:05:59

* So, so there there's lots of mechanistic data that supports the effect of insulin. So.

1:06:12

* Yeah, so, anyway, just quickly go back here. So I'll like. Just to keep to remind you that so we're focusing on on insulin and you know like insulin like growth factor is related to insulin.

1:06:21

* It's also a growth factor, but let's just. To make it simple, focus on insulin, which is, like a marker for cancer risk.

1:06:36

* Okay, and well, I'll get back a little bit to insulin, but I think it's important to understand.

1:06:45

* Festival, which is remember DMI has been used because it's very convenient to use in lots of studies but visceral fat and liver fat, Might be more directly relevant.

1:06:53

* The visceral fat is the fat that's internal like around your organs like the mainly digestive organs and the kidneys.

1:07:13

* In What in the previous life I used to. That was a pathology resident. I would do lots of autopsies.

1:07:22

* And it's amazing like when you look, you know, do autopsy and like some people have a lot of fat around it work and it's makes it like sometimes I've found it hard if you can find the case because there's so much fat.

1:07:29

* And the top is a correlated with body overall body fat, but it's not, you know, entirely.

1:07:46

* I can be some people that relatively slim. Looking that had a lot of visceral fat.

1:07:48

* And this slide gives you a sense of that. Where? This is, I think it's a CT scan.

1:08:00

* And that's why. It's hard to measure this real fat, like you can't do it like just like a questionnaire or something you need the more sophisticated measures.

1:08:10

* So what this shows, okay, this is a section, this is the umbolicus, just to give you a sense of where it's being measured.

1:08:21

* And, and these are 2 in this is just an example. I'm sure they pick kind of extremes, but I think it makes their point pretty well.

1:08:30

* So 2 individuals, the same. Body fat percentage. Age sex in the BMI of 24.

1:08:34

* And the white like is, ventures fat. That's the density to do with the CT scan.

1:08:47

* So these individuals have the same percent. So these individuals have the same percent body fat. I mean, it's not even, I mean, it's not even, I mean, big same BMI, but you know But this person has about 4 times the visceral fastest person.

1:08:56

* So.

1:09:18

* If you had to guess like one.

1:09:21

* Thank you.

1:09:25

* Is a marathon runner. One is a couch potato. Which one do you think this is?

1:09:27

* Yes, so people even like the same waste or comfort. The web circumference isn't a bad.

1:09:37

* So people even like the same wastes or comfort. What circumference isn't a bad

1:09:39

* When you look at the whole population, there's definitely a good correlation between waistcoat and visceral fat.

1:09:47

* But especially at the lower end. You do guess a lot of people that actually have high missile fat.

1:09:55

* This slide actually gives you.

1:10:03

* Which is looking at like BMI, but this is a very wide range of BMI. It has a pretty good correlation with visceral fat.

1:10:06

* So when you look at, people would have BMI of 35.

1:10:15

* Our tent, it won't be low.

1:10:22

* But you know when you get around like you know and even in the normal range You see

1:10:27

* People have almost 0 missile that people that have levels comparable to BMIs of 30. So so it's just a lot of overlap particularly in the lower end.

1:10:34

* So, and I'll explain why this is important. these are factors that increase glycerol fat, you know, beyond, obviously people would hire B and Ns will tend to have more visceral fat as we just saw.

1:10:45

* But at the lower end, particularly, it's a lack of exercise, sedentary lifestyle, probably diet, smoking actually.

1:11:00

* That being male aging is a very strong association between aging and visceral fat. In this city.

1:11:15

* For the same BMI, given the low VMI, the Asian population will tend to have higher higher visceral fat, which is why in some Asian countries like their high rates of diabetes, even though if you look at the overall BMI, they're not that, and then, you know, probably stress, I mean, there's a hypothesis having to deal with.

1:11:24

* Like cortisol in chronic stress. I mean, that could well be true.

1:11:52

* Okay.

1:11:58

* The whole literature. So there are all these factors that contribute to this.

1:11:59

* Yeah. And There's very little data that examine directly visceral fat and cancer risk.

1:12:04

* Actually I know.

1:12:13

* Some students working on that. You care about your bank. But some studies have examined visceral

1:12:16

* Positives just by CT scan so kind of like they you know things like this where they can directly measure people going in for colonoscopy and then seeing whether they have an adenoma which is a cancer.

1:12:29

* So, and this study shows.

1:12:43

* Linear association.

1:12:46

* Would add a normal risk even within the normal rank of BMI. So actually we did.

1:12:49

* With this show, this is the, you know, odds ratio, and this is a visceral fat area.

1:12:54

* And so you can see a nice linear association. And what I put here is like this is the normal range of nearby.

1:13:01

* Interestingly, most of these studies We're done in either Japan or South Korea. And most people had a DMI less than 25, so we considered that normal, right?

1:13:10

* But even within the normal range, it'd be a viceral fat is associated with cancer. You can see like people have.

1:13:22

* Levels like very low. I mean Don't worry about like what the units mean, but you have people that levels around 30 to

1:13:31

* Like, 160 or like 200. Big range of small fat and even within the normal range.

1:13:40

* You have about like, What's the fivefold difference in this year of that?

1:13:50

* I'll just. Quickly discuss discuss this. When people say how much cancer is attributable to excess body weight.

1:13:57

* Like you look at the whole population, but what you find actually is Okay, non smokers, the association is much stronger.

1:14:14

* So if you look at in the nurses in health professional study, like amongst smokers you can say.

1:14:26

* Okay, a high body mass index. Or weight gain. Like, among smokers, it only you know, contributed to 3 or 4% the cancers, but a non-smoke, it's almost 20%.

1:14:33

* Does anybody have any? Potential explanation. So the observation is that body mass index and weight gain seem to be much stronger risk factors for cancer when you look at non smokers than in smokers.

1:14:50

* Any thoughts why that might be?

1:15:09

* Okay. They're, they're, sorry, they, someone have. Yeah, that's definitely one of the contributing factors.

1:15:17

* So like smokers have You know, they're getting lots of cancers, cancers like from the smoking like.

1:15:38

* So one cancer which is probably not related to might have a small relationship to VMI, but it's typically not.

1:15:48

* So it kind of dilutes the effect. So that's part of it. Yes.

1:15:49

* Okay. And what's up? Yeah, yeah, that's actually right. I mean, It's, well, yeah, I mean, dislike I think kind of shows that.

1:16:03

* So basically, what this shows is that smoking. Actually increases visceral fat. But actually has For subcutaneous fat, which is most of the fat in your body, it has, little effect, maybe even slightly inverse.

1:16:16

* And it decreases lean body mass. So smoking is often associated with lower BMI. But actually increases visceral fat.

1:16:41

* So you actually like you know, I mean one way to think of it is that and smokers like .

1:16:53

* Not a good indicator of adiposity. Like, let's say it not smokers, BMI isn't perfect, and not smokers, BMI isn't perfect, and non-smokers BMI isn't perfect, it's not bad because it's going to be correlated with visceral fat.

1:17:02

* But in smoke, it's completely different. So I think BMI just is a bad measure in smokers I think BMI just is a bad measure in smokers of visceral fat.

1:17:11

* Okay, I'm sorry, I remember my hearing isn't too good. Yeah, right. With smoking, like some people use smoking to keep their body weight low.

1:17:22

* And then like when they stopped smoking. Like they they start gaining weight and you know smoking also reduce it like actually like my brother-in-law was big smoker and then he stopped smoking and he said I can't believe how food actually has taste. So, it's still probably better to stop.

1:17:37

* But yeah, so, it's still probably better to stop. But yeah, so, it's still probably better to stop.

1:18:05

* But yeah, so, there's lots going on with smoking. This just kind of summarizes that.

1:18:07

* You can look at that maybe, but basically, you know, I, so I actually think that .

1:18:09

* Looking at the whole population, including smokers, kind of underestimates the impact of obesity on cancer.

1:18:20

* So, so like if you, look at most estimates, which includes the whole population, like typical estimates that people come up with is 5 to 7% of cancer.

1:18:26

* Are related to smoke out of excess body weight but if you look at non-smokers probably get it more realistic estimate which is almost 20%.

1:18:40

* That's pretty bad. I have to talk quickly about physical activity. So, but.

1:18:51

* The nice thing about physical activity is that I think if you understand obesity, visceral fat and cancer, you, you understand, 80% of physical activity in cancer.

1:19:00

* These are just the guidelines. Now. The WCRF A ICR, to date only have 3 cancers.

1:19:14

* That date attribute, to lack the frisbee activity or their physical activity contributes a colon, post-menopausal breast, and end of nature.

1:19:25

* It's a it's a little bit outdated to be honest and then the other organizations list more including abreast.

1:19:32

* Something else here. And the metro esophagus kidney bladder and stomach.

1:19:44

* Again, kind of interestingly, in 2,016 there was a study, where they pulled 12 large cohort studies.

1:19:51

* So this is like, they looked at 26 types of cancer, about 1.5 million adults.

1:20:01

* This is looking at high versus low activity. You see a lot. Associated with. With.

1:20:08

* At least an association, let's not say it's causal at this point, but physical activity is more possibly associated with a lot of cancers.

1:20:15

* Now, there's 2 cancers, cross state and melanoma, where physical activity has a positive association.

1:20:24

* So being more active, people reported being more active of a virus. Does anybody have a suggestion why there's an association with prostate cancer?

1:20:31

* It's assuming that it's not causal. Yes. Yeah, that's probably very likely the recent from Melano.

1:20:35

* So it's not, you know, so I guess the message is not to not be physically active because of melano.

1:20:54

* So I guess the message is not to not be physically active because of melanoma, but to not be physically active because of melanoma, but maybe put on sunscreen, you know, take care of, you know, so, so yeah, if you're physically active outdoors, it'd be interesting to studies separate by the whether they exercise in a chair or outdoors.

1:21:03

* Got, I don't know if that's been done. How about prostate cancer? Anybody like why physical activity being more physically?

1:21:21

* I guess this would be easier after the Just guys. But that's a good thought. I think that was a hypothesis.

1:21:30

* I think, yeah, that's conceivable. I think, yeah, that's conceivable.

1:21:41

* Even though the You know, I'm not sure if that's true, but it could be true.

1:21:50

* At least it depend on type of physical activity. Probably like resistance training, I think does increase testosterone.

1:21:56

* I think like running, if anything, reduces. But it's probably to do with screening.

1:22:05

* Physically active people are more likely to get PSA tests. They'd be more likely to be diagnosed across it.

1:22:08

* If anything, they have a lower rate of prostate cancer mortality. Physically active. But you're more likely to be diagnosed with these.

1:22:18

* So. Okay, so yeah, so summarizing that slide so that there was 17 cancer types of physical activity associated.

1:22:28

* And then we talked about the positive ones. So let's look at the inverse. So, 17 cancer types.

1:22:35

* Well, that's pretty cool. It's a lot. 17 cancers. I wrote, excuse me, I wrote this up some few years ago.

1:22:49

* And, just looking at that paper and I I noted, like if you look at the cancers that are associated with physical activity is inversely associated.

1:22:59

* 17, like most. That they fall into 2 categories. Some most of them would be considered the obesity related cancer so so we're physical activity is protected with obesity as a risk factor.

1:23:07

* And then there's 4 cancers or so where are strongly related to smoking. So physical activity is related to obesity related cancers and tobacco related cancer.

1:23:29

* Now, for tobacco related cancers, did you have, you talk about this, right? No, we will.

1:23:42

* We don't talked about it yet. Right, sorry. some people think it's possible that physical activity is directly protected for lung cancer.

1:23:45

* But. There could also be a bias because like light cancer is strongly related to smoking smokers.

1:24:04

* Can't exercise that much to get one disease, which, you know, smokers who have lung disease like daphragm are actually higher risk for, lung cancer.

1:24:12

* So it's this is I think something that's really hard to tease out. It's just so strongly like, you know, you smoke a lot, you get one disease, you know, it's going to inhibit your exercise.

1:24:23

* You're at high risk for cancer. For lung cancer. So if you're in this study they looked at physical activity which seemed to be protective for lung cancer.

1:24:32

* But the only group there wasn't, well, the occupational activity was not detected for lung cancer and I also endeavor smokers.

1:24:50

* So, so this kind of argues that smoking could be a founder. So that, you know, even though you do measure smoking, it may not be measured that well or perfectly and you get lung disease anyway.

1:24:59

* So. It's possible, you know, it's conceivable there's some causality, but I think it's conceivable there's some causality, but I think it's most likely related to.

1:25:07

* Not causality. So what's most interesting is the cancers that are obesity related. I'm simple minded.

1:25:22

* I said, wow, no, every cancer practically they were physical activity is protected is also a obesity related cancer.

1:25:33

* And its physical activity is protected even if you were just for but I think there's like, is that just a coincidence?

1:25:41

* Just shows like a summary that particularly in the digestive system. Physical act this is a meta-analysis where physical activity.

1:25:54

* Associated with lower risk of almost every cancer in the digestive system. Remember insulin, you know, like.

1:26:04

* Adjustive system. This is just from the, this is just a high versus low.

1:26:16

* If you want, a, Just analysis that we did. In, 2,016 and the health professionals.

1:26:25

* This is a dose response with physical activity. And digestive system cancer. So. This is just based on the recommendations that the current recommendations.

1:26:35

* So you can see if you're handling the maximal recommendations. Which is like, you know, up to 300 min per week of moderate intensity or 150 vigorous.

1:26:47

* You get them also the benefit but you can get more benefit perhaps by going even higher. But anyway,

1:26:57

* That's a dose response. So why is physical activity related to cancer? At least I think this is likely to be the biggest reason.

1:27:09

* There could be other things, but. Just physical activity is very important for visceral fat. It's.

1:27:16

* And you can see this in these like randomized trials and prevention trials. So just slides a little.

1:27:28

* To see everything here. It's a little crooked. This is from a systematic review. This is from a systematic review.

1:27:39

* So what this shows is all the studies that they identified that had looked at exercise training like over typically like a 4 6 month period and body weight and they also measured this little fat directly like that.

1:27:47

* So what what you can see here, and that they also measured this little fact that wrapped away like that.

1:28:05

* So what you can see here, this is the percent of weight change. Body weight change. In the different trials and then this is the percent visceral What you can see is like that this is much sneaper than body percent body change.

1:28:10

* So, so just for example, let's focus on this line. So you can see So the studies that caused the about a 5% weight draw.

1:28:26

* They had about a 20 to 25% drop in this real fat. You can find some studies like this one for example where maybe it had to do with the tendency of exercise.

1:28:38

* We take it almost like very little weight change like to maybe 2%. They hardly sell wages. It saw about a 45%.

1:28:49

* So you can really reduce your visceral fat without having a big impact on your weight change. So, so I think the bottom line is that, and you know, especially if you think of people like.

1:29:05

* Remember like in that lower like people with normal BMI. I think, once a very active, again, tend to have very low visceral fat.

1:29:17

* Once they are inactive, still have pretty highness of fat. So I think physical activity can still be acting.

1:29:29

* True. That's well fat. I'll just, I'll kinda end here.

1:29:36

* I, I don't have to necessarily go through the last part there. That's bonus.

1:29:45

* So that one, you don't have to worry about that, that's bonus. So you don't have to worry about that for tests but I this is just a kind of, you don't have to worry about that for the test.

1:29:50

* But I, this is just, a kind of a take 1 min, kind of a summary slide. That basically this is almost like 30 years of my work that I've been thinking about this that can be summarized on one slide, which is kind of pathetic.

1:29:59

* That if you look at the whole body fat, I mean, and these are like averages. It's mostly your facts subcontaneous fat.

1:30:13

* So let's say it's about 90%. Vicero fat and liver fat.

1:30:26

* Liver fats also probably important for liver cancer. Because it's fatty liver, illiterate damage and liver cancer.

1:30:31

* They're actually a very small proportion of the fat. But they're also the type of fat that's very sensitive to physical activity.

1:30:39

* In value. Subcontaneous fat is much harder to change. I think a lot of people love stuff.

1:30:44

* I just can't, you know, do subcontaneous fat that much by exercise. You probably have to have a big massive reduction in date.

1:30:54

* But vessel of fat you can be affected by physical activity. And these have a big impact on information insulin resistance.

1:31:05

* Which particularly affects digestive system cancels. But other cancers too, probably contributes to breast and and then estrogen is mostly related to subcutaneous fat.

1:31:13

* In fact, there's some of Mendelian randomization studies that suggest visceral fat is not a associated with any material.

1:31:24

* It's the subcontaneous fat, which kind of makes this pretty nice model. This is very comprehensive.

1:31:34

* Like I think if you understand This slide you conceptually understand also. Physical activity and obesity epidemiology.

1:31:43

* Oh, sorry, not 2 min, so. There any questions so

1:32:00

* Does this make things clearer or more confusing?

1:32:12

* I mean the main point here is that like you can have these kind of big impacts. Like, you know, like, let's say visceral fat.

1:32:18

* Let's say a person might have, let's say, 1 kg of this world fat, which is kind of a lot.

1:32:29

* Let's say they exercise a lot and they cut.

1:32:34

* Have to have

1:32:37

* That's a dramatic.

1:32:39

* Pack that will have a big effect on inflammation in science resistance. It may not make a big impact on subcutaneous tissue.

1:32:41

* They may actually even gain some lean mass. So you won't see much of a difference on body weight.

1:32:50

* So. But

1:32:55

* Okay.

1:32:58

* Most of the effect.

1:33:06

* So like the effect of physical activity could still be mediated largely through things like this or or

1:33:22

* Padded catapults. We don't have

1:33:28

* Okay.

1:33:31

* Like the If you look carefully at the epidemiology of physical activity. And cancer, I think you can explain a lot of it. This concept. And there could be other things going on.

1:33:39

* I mean, if people study physical activity, they don't wanna make it too simple specific markers like immune system things like that which you know could be relevant but I really think that this is looking broadly at the literature this kind of, most of what's going on with physical activity.

1:33:56

* There's Maybe.

1:34:18

* At least by population, what people do.

1:34:19

* Is much more

1:34:20

* But resistance would have some of the effects too. We've actually booked that in our data. You see pretty

1:34:21

* The correlations with resistance strengthening and Lord.

1:34:22

* Something like that. So yeah, either one, but mostly I think a class might be waiting. I'd be happy to.

5.

5

* Kresge 502 Cart: We have. Unfortunately, I think, Covid and other respiratory infections running rampant. And so we have people who are going to be joining. I hope you all stay healthy and tough times.

0:12

* Kresge 502 Cart: We've always gotten struck with all sorts of things in this class. So before we get started, and we have an amazing guest lecture. Today, we're gonna start out with our usual cancer epitia. Today's question is which of the following cancers has the lowest estimate of heritability. And if you remember, heritability is the relative contribution of inherited

0:27

* Kresge 502 Cart: genetic factors to the incidence of cancer. Is it a noma B prostate cancer, c, testicular cancer or D colon cancer. So which one has the lowest estimate of heritability

0:52

* Kresge 502 Cart: of the lowest, relevant genetic fibers

1:08

* say.

1:28

* Okay.

1:30

* Kresge 502 Cart: do you know the answer? No

1:36

* Kresge 502 Cart: melanoma's in the clear lead right now.

1:43

* Some of them voted for testicular cancer.

1:49

* Kresge 502 Cart: Testicular cancer is a fascinating cancer. I don't think, unfortunately, anyone signed up for it for the project. But it's a really interesting cancer. All right, let's give it about 10 more seconds

1:53

* Kresge 502 Cart: and 5 more seconds, 3,

2:07

* Kresge 502 Cart: 2, and one great so the the melanoma and prostate cancer actually are tied for the 2 cancers that have the highest estimate variability. I know we haven't had our prostate cancer lecture yet, but they're the 2 cancers that seem to have the strongest genetic contribution based on family based studies and twin studies, which is quite interesting. Conrad stops up when he lectures. We'll talk about prostate cancer. Melanoma is interesting.

2:13

* Kresge 502 Cart: and I think part of that heritability or in her genetic factor around things like genes that put people at different predisposition to sun exposure, probably, I think, but there may be other genetic variants as well in the moderate level. It actually has a really strong family history.

2:46

* Kresge 502 Cart: A person has a brother or a father who had cicular cancer. Their own risk of Cisco cancer is substantially elevated. About half of that family history is actually due to some shared environmental factors. Interestingly, so, it's an interesting cancer that way that a lot of times we think of family history as being such a strong genetic susceptibility. But into circular cancer, the family history, a big chunk of

3:11

* Kresge 502 Cart: is actually due to shared environmental factors and then genetics. And then so colon cancer ends up being the cancer with the lowest estimate of heritability.

3:36

* Kresge 502 Cart: Probably the 10 major cancers. I think so Colon and rectal cancer together. Step one. Cancer also has a relatively low estimate of heritability. So great, excellent! Introduce.

3:47

* Kresge 502 Cart: Don't say too much.

4:02

* Yeah. Yeah.

4:27

* Kresge 502 Cart: I was lucky to get me young as my student he was a great, great student, but now he's already he's progressed rapidly. He was

4:34

* Kresge 502 Cart: like after he, when did you graduate? 2050? Nk, yeah. So then he was at the went to Mgh. Mass. General hospital, but also has connection to school public health, as you can clearly see there. And last last year he was promoted to associate Professor. So he's obviously doing. Great. He he's

4:43

* Kresge 502 Cart: does a lot of work on colorectal cancer. And he has, like broad base knowledge and like microbiome metabolomics, basic epidemiology.

5:07

* Kresge 502 Cart: and does other things besides colorectal cancer. But that's one of his primary areas. And I used to give this lecture. And then few years ago, he started taking over. We was getting better comments better. So I said, Okay, you have to stop giving the lecture. So

5:21

* Kresge 502 Cart: thank you. Thank you. Introduction now. So it's really my great pleasure to be here. I remember the last time I was in this classroom, I mean as a student was actually for the cancer epic class speaking when Dimitri was giving the liver cancer. Yeah, it was one of the most impressive lectures that I have ever taken.

5:40

* Kresge 502 Cart: So it's great to be back to this class. And as I mentioned, I've been lecturing for the class for a few years. I learned something new. Actually, I just learned something new from the question. It's actually good, because I was deciding to cut.

6:05

* Kresge 502 Cart: although last year as well. So I actually covered a genetic lecture because the genetic variance that we have identified seem to have pretty modest situation with colon cancer. That also makes sense that colon cancer is at least heritable among the major ones. So anyway, let's get started.

6:29

* Kresge 502 Cart: This is outline for today's talk. I first want to briefly talk about the descriptive epidemiology of Colorado cancer. So this is the most updated data from the American Cancer Society regarding new cancer cases and death phase in this country, as we can see here.

6:53

* Kresge 502 Cart: we can see here colorectal cancer ranks. The third in both men and women, and also for both incidents and mentality. And it comes for about 8 to 9% of deaths among all cancers. So it's definitely still a major cancer in this country.

7:17

* Kresge 502 Cart: So this shows the trend of coronal cancer, incidence and mortality in the United States. In the past few decades, as we can see, luckily both incidence and mortality have been declining. So this is encouraging. However, as we can see here, the reduction in mortality is

7:38

* Kresge 502 Cart: much slower than that, for instance. So, as you may have learned from Epqer one, so that leads to higher prevalence, that means there is a growing number of individuals living with colon cancer in the country. So in the most recent report, there is about 1.1 million Americans living with cancer in 2,016, which represents a 20% increase compared to

7:58

* Kresge 502 Cart: so addressing the increasing number of the staff efforts is a huge is a huge concern in the cancer research community, especially for colon cancer. And I will touch on that later. So regarding the reasons for the decline for both incidence and mortality in this country. So this is a result based on the simulation analysis

8:28

* Kresge 502 Cart: processes from a calorie risk from 1,975 to 2,000. So it's a little bit old, but still I think the numbers probably still holds, as we can see here, according to the model estimates.

8:52

* Kresge 502 Cart: Now, 53% of the reduction is likely due to screening. So colonoscopy screening has been increasingly used in the country, and the screening uptake has been gradually growing as well, so we'll talk more about that later and risk factor. Improvement also accounts for about 35% of the decline, and this is mainly driven by the reduction in smoking

9:06

* Kresge 502 Cart: and also other unhealthy lifestyle. And there's also additional contribution of treatment about 12%. So this is from epneuric data. And if you know about economic analysis. Actually, the treatment actually consumes the largest of

9:37

* Kresge 502 Cart: the economic burden for colon cancer. But compared to the risk factor and the screening, it actually contributes the least. So this highlights the importance of prevention.

10:01

* Kresge 502 Cart: And interestingly, for colon cancer among young individuals below age 50, there is a growing increase, as you can see here for the older individuals, for age 40 to 64, and for about 65, there has been a decline. But for young individuals

10:13

* Kresge 502 Cart: there has been an increase since, as you can see here, this patent holds for both men and women, and you probably have read from the news like from the press. There is a huge, a lot of discussion about what is driving this increase. The answer is, we still don't know. And this is a big question to be addressed.

10:37

* Kresge 502 Cart: And interestingly, it's not just like America. It's across the globe, even for some middle or low income countries. There is also an increase in early onset colored cancer, and specifically in this country some notable demographic differences.

11:02

* So it seems like the instance of early onset called a retro cancer, which is defined as cancers

11:24

* Kresge 502 Cart: diagnosed among individuals aged 50 or younger. So it has been stable among blacks and Hispanics, but there has been a substantial increase in non Hispanic whites, and also it varies by state, and the increase is most predominant in Western States, such as Washington and Colorado.

11:31

* Kresge 502 Cart: Very interesting talent can I say, yes, is it? Was it because of those rates were already lower? And so they had more growth to grow? Or is it something else? Yeah, that's part of the reason, because, like the Western States tend to have lower rates in general as a southern stage, have much higher rates. Yeah.

11:55

* Kresge 502 Cart: yeah, I think it's very interesting for Colorado, I remember from the obesity IP like it has the lowest obesity. So it's interesting.

12:22

* Kresge 502 Cart: And here I really want to highlight. It's not just the age. It's actually also a birth cohort effect. So this is a figure from a recent review on this topic. It shows that in this ratios of Colardo cancer by birth cohort across different regions in the world, using the birth cohort of 1,950 as a reference.

12:35

* Kresge 502 Cart: As we can see here across all regions there has been an increase after the 1,950 birth cohort.

13:00

* Kresge 502 Cart: and here the increase is actually most dramatic for East Asia.

13:11

* Kresge 502 Cart: And if we look at the age and birth cohort effect together, this is data from again from the United States, from the American Cancer Society. So the X axis is a birth cohort, and the different color represent different age groups.

13:18

* Kresge 502 Cart: as we can see, still, like after age. First of all, I want to measure this is 50 to 54 group. So we can see there's also a slight increase

13:37

* Kresge 502 Cart: for the older, for the more recent birth cohort compared to the older, like birth cohort. So again, it seems like it's not just the age. So there has been some projection that over time as the new birth cohort ages. We will also see an increasing instance of

13:52

* Kresge 502 Cart: Colorado cancer even among older individuals.

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* Kresge 502 Cart: And again, we can see there seems to be an increase after the birth cohort. So I really want to put this out, because I know there has been a lot of discussion, a lot of coverage on early onset cholesterol cancer. But as an epidemiologist, I hope you can understand. It's not just the age. It's really a birth cohort, in fact.

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* Kresge 502 Cart: so especially because screening is normally recommended for individuals at age 50. So the screening has kind of cut a lot of the older onset of colorectal cancer. But still over time, we still see a growing increase, a green increase in colorectal cancer

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* Kresge 502 Cart: across age groups are for the more recent birth cooper.

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* Kresge 502 Cart: So this, this epidemiology data seems to suggest that there must be something related to the birth cohort like to the environmental changes over the more recent birth cohorts. So here are the like

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* Kresge 502 Cart: possible reasons that have been proposed in the literature, including unhealthy lifestyles, such as obesity, Western diet, and lifestyle, and also there is a strong interest in studying early life exposures. This is particularly relevant to early onset cholera, because for younger individuals their exposure history is much shorter, and the critical period, maybe.

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* Kresge 502 Cart: is more likely to be in the early life period compared to older onset cancers and also the environmental change. We know that the environment has changed dramatically over the past few decades. So air pollution and climate change related climate change issues that may also play a role. And also I'll talk more about the microbes later. It can be

16:02

* Kresge 502 Cart: considered as a marker of the environmental change, because macrobound is very responsive to the environment, and any changes in the environment can be imprinted in the microbound. So by studying macrobound, we can get a lot of information about the environmental exposures.

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* Kresge 502 Cart: Any questions so far.

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* Kresge 502 Cart: Ok, oh, yeah. So you just mentioned that I can cover environmental changes. I was just wondering to what extent

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* Kresge 502 Cart: I know there's a lot of talk to them being exposed to just food. Yeah, yeah, that's a good question.

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* Kresge 502 Cart: I will talk more about this later. That for microbound, our understanding is still very premature. It's still a green area. But I think, like the more we study, the more we realize, like how individualized macrobound is. So that really suggests that it's the totality of the environment that really shapes the microbiome. I mainly focus on the gut microbound.

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* Kresge 502 Cart: and there has been very compelling data really indicates that a variety of exposures that lifestyle medication, environmental exposures can all influence the microbes. And if we look at each individual factor, the impact is very small. So that's another tricky thing with microbes effective for individual

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* Kresge 502 Cart: factors is very small. It's the totality of the environment that really shapes the.

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* Kresge 502 Cart: So next, I want to briefly talk about the molecular features and the natural history of colorectal cancer. So among all cancers, colon cancer is probably the best characterized cancer molecular. So there are 2 major pathways for the development of polaroidal cancer. One is the chromosome or instability Pathway.

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* Kresge 502 Cart: which is characterized by multi-step genetic mutations. It starts with Apc. And then Kras and smite 4, and also PP. 53. And there is an increase in the chromosome instability over the natural history

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* Kresge 502 Cart: is the microsatellite instability. So the 2 pathways are very different molecular. So the macrosatellite instability pathway is characterized by the activation of the DNA may match repair genes.

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* Kresge 502 Cart: and also the related hypermethylation. So cancers developing through this pathway is characterized by microsatellite instability and also hypermethylation.

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* And for colon cancer.

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* Kresge 502 Cart: The natural history evolves from normal epithelium to adenoma and then to cancer. And these 2 different pathways also contribute to histologically different praker solutions, like different adenomas like for the microsatellite instability pathway, it is underlying the development of the surveillance

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* Kresge 502 Cart: of the years to be called a serenity Adenomas, and which is very different from conventional adenoma which develops through the chromosomal instability pathway. So

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* Kresge 502 Cart: again, it really highlights the heterogeneity of Colorado cancer.

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* Kresge 502 Cart: not just molecular, but also risk of actor wise. We will see that later.

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* Kresge 502 Cart: Yeah. So the microsatellite instability pathway is also called a serrated pathway, because it's characterized by the precursor illusion, serrated columns.

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* Kresge 502 Cart: So next, I want to spend some time going through the different provision strategies, and also by talking about the risk factors for colorectal. As an epidemiologist, this is probably the most important and the most interesting to us.

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* Kresge 502 Cart: So for primary prevention, as you must have learned, it's about prevent cancer from occurring.

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* Kresge 502 Cart: So here for the risk factors, we have been focusing on diet lifestyle and medications.

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* Kresge 502 Cart: So here is a summary of the factors that have been shown to increase risk of colorectal cancer.

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* Kresge 502 Cart: including smoking alcohol obesity, sedatory lifestyle. Red are processed meats and Western diet in general.

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* Kresge 502 Cart: So before I go over the individual risk factor, I just want to show this study. This was the study I did during my final year of the Phd with Ed, so we look at the potential

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* Kresge 502 Cart: preventability of cancer, including collateral cancer by lifestyle modifications. So we considered the 4 major lifestyle factors, including smoking alcohol obesity and physical inactivity, and we calculated the population attributable risk by comparing the high risk group versus a Low Risk group. So the Low Risk group is defined by

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* Kresge 502 Cart: a combination of all these 4 different different, like

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* Kresge 502 Cart: risk factors. And we can see here in our nurses, health study and health professional phlog study. We found about a 20 to 30% difference in terms of the incidence of collateral cancer in men and women, and we know that the nurses and Hpfs, as you probably have learned from this class or other class. It's

22:29

* Kresge 502 Cart: the participants are all health professionals, so they tend to have healthier lifestyle. So we also compare our population to the US. General population that compare Bring the Low Risk group in the cohorts to the US. General population. As we can see, the Pr increased to 40 to 50%. So this suggests that a large

22:53

* Kresge 502 Cart: proportion of colato cancer instance, can be prevented by simple modification of these lifestyle factors. So again, colorectal cancer is probably one of the cancers that is most strongly associated with these lifestyle factors. So it really highlights the huge potential for prevention of colon cancer.

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* Kresge 502 Cart: So next, I will briefly go over individual risk factors. This is

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* Kresge 502 Cart: the result of smoking was actually the study that had the data almost 30 years ago.

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* Kresge 502 Cart: But it shows that the relationship between years since starting smoking in relation to Colonel cancer risk. And we can see that there is

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* Kresge 502 Cart: nonlinear relationship. The risk of increase did not emerge until the years 35 to 39.

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* Kresge 502 Cart: So this indicates there's a long latency period for the smoking effect on colon cancer. So there's roughly, like a thirty-year induction period for smoking.

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* Kresge 502 Cart: And also.

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* as I mentioned earlier. Colloidal cancer is very heterogeneous. There are different pathways. So if we look at smoking in relation to in relation to different subtypes of colored cancer. We can see that for overall colito cancer. It's pretty modest. The effect size is only 1.2 a for the highest category

24:42

* Kresge 502 Cart: compared to never smokers. But when we classify tumors into different subtests, we can see the red risk is much more substantial for certain molecular subtypes of colored cancer specifically for same high cancer and Msi high cancer. These are the cancers that are considered as serrated cancers that are available through the serenity pathway.

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* Kresge 502 Cart: As I mentioned earlier, the serrated pathway is characterized by hypermethylation and also being deficiency. So we can say there is a very strong relationship indicating that the potential role of smoking in damaging the mismatch repair pathway.

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* Kresge 502 Cart: Maybe the numbers are small. But do you also does it also take that decades long time for Msi cancers that happen, or do they happen? That's great question. Yes, I think substantially, there is data suggesting that

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* Kresge 502 Cart: cerebral cancers tend to divide more rapidly compared to the conventional cancers.

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* Kresge 502 Cart: I will also show some some data later about that. So similar findings have been found for precursor solutions. So here we look at serrated pollens versus conventional Adenoma. As I mentioned earlier, the conventional anoma is considered as the precursor solution for the chromosomal instability pathway, whereas the accelerated pollen is

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* Kresge 502 Cart: precursor for the serrated pathway we can say the association with smoking is much more substantial for serrated pollen compared to convention and normal. So this has clinical implications because the cancers with the serrated features have been identified.

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* Kresge 502 Cart: have

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* Kresge 502 Cart: seem to have a like. The serrated, serrated cancers are more likely to develop after negative colonoscopy.

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* Kresge 502 Cart: This is also related to Laura's question. Like patients with a negative colonoscopy may actually develop a cancer

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* Kresge 502 Cart: very like quickly after the negative exam. So this, like I said, Msi has been characterized

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* Kresge 502 Cart: has been shown to be present in these serrated cancers, and this suggests that for smoking, because smoking is so strongly associated with serrated cancers, it really suggests the potential of prevention for individuals who had a negative colonoscopy to really stop smoking because smoking can

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* Kresge 502 Cart: player can really promote the development of surated cancers, even after an active exam. And unfortunately, we look at our data. And

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* Kresge 502 Cart: for people with

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* Kresge 502 Cart: colonoscopy screening, very few change, like very few participants, really change their lifestyle after the screening, especially for those with an active screening. So there's a long way to go if we look at the risk factor data in our cohorts

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* Kresge 502 Cart: like it doesn't really change much even after people having a positive colonel space screening. And again, this really highlights the potential of epidemiologic data to kind of inform clinical practice.

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* Kresge 502 Cart: not just for our biological understanding, but also for clinical translation and for alcohol. This is a data from the pooling project of 8 cohort studies looking at different dose of alcohol intake in relation to colon cancer risk, we can say again, there seems to be a nonlinear relationship.

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* Kresge 502 Cart: So there is no increase in risk until roughly, like 30 grams per day of alcohol consumption. This is roughly about 2 drinks per day. So for alcohol to influence colorectal cancer. There seems to be a dose like a threshold effect.

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* Kresge 502 Cart: And for Bmi there has been a lot of studies looking at obesity in relation to colorectal cancer. This is a meta analysis summarizing the results, we can see that there is association for both men and women, although for men the association is much stronger than that for women, so the relative risk is about 1 point

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* Kresge 502 Cart: 10 per 5 kg per square meter increase in the mi.

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* Kresge 502 Cart: and this sex difference has been well documented in the literature, not just for colon cancer, but also for other obesity related cancers. And we are still studying what is a mechanism? What is the potential reason for the sex difference? One reason for colon cancer may be related to sex hormones, which I will talk more about that later.

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* Kresge 502 Cart: and in addition to overall, the visual ad central obesity may also have some independent effect. So this is a study that we did. Looking at the Drone Association of Bmi and with conference with cholera cancer risk in women and money. So we classified individuals according to both Bmi

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* Kresge 502 Cart: and also with this conference we can see that for women we didn't see any statistical, significant association. But for men we can see within each Bmi group

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* Kresge 502 Cart: linear relationship for witness conference. A higher waste conference is associated with increased risk of coronal cancer within the same emi category. So this indicates the additional value of facial adiposity for colon cancer.

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* Kresge 502 Cart: and a similar pattern has been shown for other cancers as well.

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* Kresge 502 Cart: So for physical activity. It is also an established protective factor for coloreto cancer. This is a good analysis, and that was originally published. Interestingly, the association is predominantly observed for colon cancer, but also for rectal cancer, for rectal cancer

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* Kresge 502 Cart: not statistically significant, and when the authors looked at moderate versus vigorous agusting, both had an inverse association. But the association is stronger for vigorous, vigorous activity compared to moderate activity. And this is after mutual adjustment

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* Kresge 502 Cart: suggesting that the different effects of different activity tasks.

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* Kresge 502 Cart: and the second rate behavior has also been associated with higher risk of colon cancer. This is the result from the analysis looking at total saving time, TV billing time and also occupational saving time.

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* Kresge 502 Cart: So we can see for all 3 exposures there is a positive association. And interestingly, the association is much stronger for digital colon cancer compared to rectal cancer. And it's pretty weak for proximal colon cancer.

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* Kresge 502 Cart: So digital colon cancer is includes the cancer studies in the like

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* Kresge 502 Cart: after the the splendid flexure descending, cooling, sigmoid and proximal cooling includes the ascending cooling and the transfers, and also the sick. So there has been a lot of etymology data indicating the molecular and risk factor difference across the subset.

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* Kresge 502 Cart: and this subset difference also is also associated with the molecular profiles, so the storage cancers are more likely to develop in approximal coding, and the conventional cancers are more likely in the digital coding. So

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* Kresge 502 Cart: the general like conclusion is that thisal colon cancer is most generally associated with

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* Kresge 502 Cart: lifestyle factors, particularly the metabolic risk factors, including obesity, secondary lifestyle, and the proximal colon cancer has been most strongly associated with smoking and some inflammatory risk factors. So there's a lot of

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* Kresge 502 Cart: like heterogeneity within collateral cancer. That's how the molecular technology can be really helpful.

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* Kresge 502 Cart: So for western data, again, we can say that western data is much more strongly associated with distroin cancer, and then rectal cancer and proxy

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* Kresge 502 Cart: trading week. An Association party week.

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* Kresge 502 Cart: and among Western diet repelling red and processed meat is the strongest risk factor, particularly for processed meat. As we can see from the Meta analysis, the right risk

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* Kresge 502 Cart: is very high for processed meat compared to Rami, I mean for RAM meat there are still some positive associations, although the aftermath is less consistent compared with that for processed meat.

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* Kresge 502 Cart: So to summarize, this is from the review that others wrote few years ago regarding the mechanism so like the unhealthy data lifestyle sent to be in promoting cholera cancer by the insulin and Igf one pathway. So this all health

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* Kresge 502 Cart: lifestyle factors can increase the production of insulin and also the higher level of Igf. I. Both of these hormones can induce cell proliferation and reduce apoptosis that can promote cancer growth.

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* Kresge 502 Cart: So this is the.

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* Kresge 502 Cart: I would say, a pretty well-established pathway. But there is also other pathways that also play a role such as the inflammation and the microbound.

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* Kresge 502 Cart: So is there any questions about the risk factors?

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* Kresge 502 Cart: Okay, so next, I want to briefly talk about the factors that may decrease risk of collateral cancer. Here are there major factors that have been studied, including vitamin d calcium for a fiber aspirin and a hormone replacement therapy, and therefore the 3 factors with a star that indicates the evidence from randomized

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* Kresge 502 Cart: clinical trials. In other words, these 3 factors have been pretty well established to have a protective effect on colored cancer.

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* Kresge 502 Cart: So just briefly going through each of them. For Nvd, the original hypotheses actually comes from the ecological study. So there was the vision that people living in the South America are less likely to develop color compared to people living in the northeast.

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* Kresge 502 Cart: like in the north, particularly northeast. So

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* Kresge 502 Cart: And then that was hypothesis when Med was hypothesized to be a potential factor

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* Kresge 502 Cart: in the mentality. And then, after that, there has been numerous epidemiological studies assessing the binding levels in cohort studies. So this is a recent publication from the International Pooling project that includes 17 cohorts that measure levels among over 5

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* Kresge 502 Cart: cancer cases. We can see that there is a general inverse relationship between binding D levels and cancer risk.

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* Kresge 502 Cart: Here I also included the Institute of Medicine Guidance for bone health. Regarding Bambidi status for people with deficient and insufficient they tend to have a higher risk of cancer compared to individuals with sufficient or even higher

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* Kresge 502 Cart: 2,

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* Kresge 502 Cart: and a similar inverse association has been observed for calcium. For calcium. There seems to be. There seems to be a nonlinear relationship, as we can see here the benefit of levels of at about 1,500 microgram per day consumption.

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* Kresge 502 Cart: So after that the risk did not continue to decrease.

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* Kresge 502 Cart: and for foli there is a very interesting latency effect. So if we look at the Folate intake of prayer to colorectal cancer diagnosis there is no association. The lamp is pretty flat, but when we look at when we look at the intake

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* Kresge 502 Cart: 12 to 16 years prior to diagnosis with a pretty substantial inverse association between higher folate levels for higher foliage intake and lower cholesterol cancer instance. So this indicates that it is folate intake that is.

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* Kresge 502 Cart: decades before that really influenced cancer risk. In other words, if we want to prevent colorectal cancer by fully supplementation or other method. The supplementation has to happen early.

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* Kresge 502 Cart: much early in life in order to have to say benefit like Wow. years later.

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* Kresge 502 Cart: and the fiber is another beneficial mutual nutritional factor that has been linked to colorectal cancer. Instance, as we can see from this analysis, there's about 10% reduction for each 10 gram per day intake of divergent fiber. And we can see that the association is pretty consistent across studies, especially for studies with larger sample size.

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* Kresge 502 Cart: And there's also a pretty linear relationship in the dietary, fiber intake and cancer. Instance.

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* Kresge 502 Cart: if we put intake particles in this graph, like the average intake in this country, is about 16 grams per day, which over here the recommended intake is 28 to 34 grams per day, which is over there, and as we can see if we increase the fiber intake for everyone to the recommended level, there can be a substantial public health impact on colonial cancer prevention.

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* Kresge 502 Cart: So this is just to show you the potential of primary prevention for colon cancer, even for a single battery factor.

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* Kresge 502 Cart: If you I didn't touch on the mechanisms. But if you want to learn more about how this nutritional factor may influence colon cancer risk. You can refer to the review that we wrote a few years ago, summarizing all the different pathways.

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* Kresge 502 Cart: And also I want to mention that for these nutritional factors the observational data have been pretty compelling also quite consistent. But for the clinical trials. As you may have learned from the media, from the literature, the evidence is less clear, so most the nutritional innovation studies did not actually say, a benefit

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* Kresge 502 Cart: for cancer prevention, including for a calcium and even fat, maybe D. So here are some of the reasons that

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* Kresge 502 Cart: we should be very careful about like when we interpret the findings for the clinical trials. So one reason, maybe the appropriate time window of intervention. So most of the individual studies for Colon Cancer Prevention have enrolled patients with a history of polyps. So, as I mentioned earlier, Pollux is a precursoration of colon cancer. Individuals with polyps

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* Kresge 502 Cart: have already had the carcinogenic process started. So we may have missed the critical time of cancer initiation. This is particularly true for Folate, because it has been shown that if we give patients with an enormous foliage supplementation supplement.

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* Kresge 502 Cart: they actually have a higher risk of developing colonial cancer. So it's possible that Poly may actually promote the cancer development among individuals with early precursor issues. In other words, among individuals whoseogenic process has already started giving them folly can be harmful rather than beneficial.

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* Kresge 502 Cart: and another reason is inappropriate dose. So for one, maybe the dose that was used in the Who, which is one of the largest intro trial in nutritional studies women's health initiative. So they use the 400 Iu per day. And

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* Kresge 502 Cart: this is actually very small, like, if we look at the plasma vitamin D levels. The 400 IU only increase only lead to a very modest increase in plasma levels. And that's why the more recent vital study, the vitamin d. And facial oil trial used as a 2,000 iu.

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* Much higher dose to test whether there's any benefit. And another reason may be because participants

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* Kresge 502 Cart: already sufficient in their intake for these nutritional factors, for example, for calcium in the who in the Women's Health Initiative, their baseline intake is already over. The 1,000 micrograms per day dose that I showed earlier after 1,000 micrograms per day. There's actually no further reduction in credit

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* Kresge 502 Cart: concern in space. In other words, if all individuals start here, if we give them calcium supplementation, we won't be able to see any benefit.

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* Kresge 502 Cart: And finally, like most of the clinical trials, have very limited duration less than 5 years, so they show the duration may not be sufficient to observe benefit, especially for factors that have a long latency period, such as folding. So this is just some considerations

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* Kresge 502 Cart: to to to take into account when we interpret the observational findings versus the innovation results. So as etymologists just don't. We shouldn't just take the results at a Facebook value. And really to need to think about the alternative interpretation and to

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* interpreted the totality of the literature

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* Kresge 502 Cart: there any questions or comments about it regarding this.

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* Kresge 502 Cart: this is very relevant to the the the talk that Ed gave on diet and cancer. So I'm wondering also kind of given the conversations about the different studies design, so do you have any other thoughts, or that where you might see differences between the Rcts and epidemiologic studies.

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* Anything else that you can think most.

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* Kresge 502 Cart: Yeah, I have. Probably I have already mentioned this, like for medication. Clinical trial is probably the good standard. But for nutrition there's a lot of problems with the clinical trial, and we really should be very cautious. Yes.

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* Kresge 502 Cart: is that adjusted for anything. I don't think so. It's just that it's age adjusted. But other than that, it didn't adjust for anything

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* Kresge 502 Cart: like even more different diet.

48:02

* Kresge 502 Cart: not to generalize regions. That's good point. I'm I'm not sure. I mean, this is a historical data, right? From 1,900 seventys to 1,990. And since then, like I mentioned earlier, a lot of things have changed. I actually, I can't remember. I need to check if the pattern still remains nowadays.

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* Kresge 502 Cart: Attitude right?

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* Kresge 502 Cart: It's a bit weaker now, but it could be related if it is actually the sun

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* Kresge 502 Cart: that the patterns of sun exposure got very different. 19 sixties.

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* Kresge 502 Cart: Yeah, just I feel like,

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* Kresge 502 Cart: At that time. Probably there seemed like more. I mean, the epidemiologic pattern has changed very dramatically over the past few decades. But still I feel like the ecological study can be really beneficial to

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* Kresge 502 Cart: get some initial clue like, especially for early onset cancers. Since we really don't know the reason this kind of ecologic study can be beneficial or can be helpful for hypothesis generation.

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* Kresge 502 Cart: Besides the diary factors, some medications have also been linked to lower risk of colon cancer. Aspirin is the most established medication. As we can see, this is from a pool analysis of fat, randomized, controlled trials. We can see there is a very strong diverse association

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* Kresge 502 Cart: between aspirin use and a lower risk of colon cancer, and the Association is much stronger for proximal colon cancer. Again, this goes back to my earlier comment regarding the subset difference, the proximal colon cancer is more related to the serrated pathway and more related to the inflammation, inflammatory mechanisms. So this

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* Kresge 502 Cart: it fits in pretty well, like aspirin, may reduce the risk of proximal coral, and also, when we look at the treatment duration we can see here.

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* Kresge 502 Cart: like only like the inverse association, was only from for the trials with at least 10 years of treatment. So again, it highlights the latency effect for aspirin as well. It takes about 10 years to really see a benefit. Similarly, as we can see from this study, the women's health study, which is a large, randomized, controlled trial with 100 microgram

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* Kresge 502 Cart: per day. This is considered a low dose, and also alternate alternate day as per use. We can see that it takes about 10 years to really see a separation between the intervention group and the control group.

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* Kresge 502 Cart: So the solid line is Aspirin Group, and the dash line is a control group, and we can say that 2 lines did not separate until 10 years

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* Kresge 502 Cart: after the invention. Again.

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* Kresge 502 Cart: it highlights the the importance of having long duration in order to see a benefit for this

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* Kresge 502 Cart: protected factory, and you may have learned from the the press. There's also a concern about like aspirin use among other individuals. So this is from the recent aspirate trial. This study enrolled patients who are like

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* Kresge 502 Cart: at least 70 years old, so they wanted to say whether they should also take aspirin because aspirin can be beneficial for colon cancer and also for cardiovascular disease prevention, and for older individuals is very poor. So they conducted this large randomized control to test the benefit of aspirin use

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* Kresge 502 Cart: among all the individuals, and we can see here. Interestingly, the Aspirin group actually had a higher risk of cancer death compared to the placebo group.

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* Kresge 502 Cart: and and as a positive association was observed for many cancers, including collaborative cancer. As we can see here, the relative risk is pretty high is 1.7,

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* Kresge 502 Cart: and because of this result, in 2,022. The US. Preventive Services task force no longer recommends aspirin use for colato cancer prevention like before 2,022. The recommendation was to use aspirin for prevention of colon cancer among adults.

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* Kresge 502 Cart: even average risk adults. But because of this funding the Uspsf. They stopped the recommendation for Colon cancer prevention, although we know that the evidence comes from old individual and does not apply to the young adults.

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* Kresge 502 Cart: But still the recommendation changed dramatically. And also.

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* Kresge 502 Cart: Another reason is because of the bleeding risk. Aspirin is associated with higher risk of bleeding, particularly gi bleeding. So the the I guess the task force was very cautious about this, and no longer aspirin.

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* Kresge 502 Cart: and completely for all individuals, regardless of being at higher risk for colon cancer. For Cbd there is still recommendation for the high risk.

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* and I mean we still don't know why, like what is causing the increase among older individuals.

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* Kresge 502 Cart: Whether this is related to the biology, or how aspirin works in older individuals versus young individuals. It is related to the characteristic of the participants in this clinical trial, and there will be longer follow up, and the trial is still under active follow up. So there will be more data

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* Kresge 502 Cart: after longer. Follow up time, because the the the

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* Kresge 502 Cart: the the unit. And the publication was people like roughly after 6 years of information.

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* Kresge 502 Cart: So another medication that has been linked to lower risk of colon cancer is the hormone replacement therapy, as we can see from the Women's Health Initiative, a large clinical trial. Comparing the effect of estrogen plus progester versus placebo. We can see there is much lower

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* Kresge 502 Cart: colonial cancer instance in the treatment group compared to the controls.

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* Kresge 502 Cart: And there has been

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* Kresge 502 Cart: really well documented biological pathways regarding how estrogen may actually protect against colorectal cancer through the estrogen receptor which is widely expressed in the colorectal mucosa. And this may actually explain some of the sex difference in cancer risk factors, women, especially the post menopausal women.

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* Kresge 502 Cart: Their major source of astrology is from the adiposity from the adipose tissue, so that may explain why, obesity is

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* Kresge 502 Cart: much weekly, very weekly, associated with colon cancer compared to that in mind, so the estrogen may offset some of the adverse effects of obesity.

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* Kresge 502 Cart: and then another emerging risk factor is got macrobound. You probably have learned before that macrobound is considered as another organ of our human body, and it plays an essential role in both the metabolism, immunity, and also in adaptory

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* Kresge 502 Cart: absorption. So that's why we propose that this kind of triangle model and a way

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* Kresge 502 Cart: hypothesized that it is the interplay between diet microbes and the host factors that together determines cancer risk. This is particularly true for colorectal cancer. Given that the largest number of bacteria in our human body lives in the gut.

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* Kresge 502 Cart: and there have been some microbes linked to a higher risk of colon cancer and some linked to lower risk of coronal cancer. And here, at least, the bacteria that have established to play a role in colon cancer development.

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* Kresge 502 Cart: And right now the evidence from under microbound is largely from retrospective studies like a piss control study. We still don't know whether microbound changes are a cause or a consequence of colon cancer development.

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* Kresge 502 Cart: That's why we are establishing a prospective cohort in the nurses have studied 2 trying to understand the role of the baseline, how it may predict subsequent risk of colorectal cancer and other diseases. So we are collecting macrobound samples from women in the nurses have studied 2 cohort.

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* Kresge 502 Cart: and because these swimming are still under active follow up. We will have instant cancer cases after still an oral sample traction to prospectively study the role of microbes in cancer development.

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* Kresge 502 Cart: So I can imagine there will be more fundings coming up in the last few years from the school.

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* Kresge 502 Cart: So that's all for primary prevention. If there are any questions about the risk factor or protective factors.

59:15

* Kresge 502 Cart: Okay? If not, we can move on to the secondary prevention, which is about a screening basically to detect the cancer early for

59:28

* Kresge 502 Cart: detect and also remove the detector cancer early and then remove the precursor lesions, so called parlors. So this is data from the observational studies looking at colonoscopy screening in relation to colorectal cancer, incidence, and mortality, we can see that there is a very strong inverse association for both incidence and mortality.

59:38

* Kresge 502 Cart: Sorry. These are based on epidemiological data clinical trials. Yes, yeah. And this is from clinical trials. This is from the Nordic trial, which was, I think, published in 2,022. It's a very interesting study design. They use the pragmatic trial, basically the grandma's individual first.

1:00:02

* Kresge 502 Cart: and then they only consent. Individuals who are randomized into the intervention group.

1:00:27

* Kresge 502 Cart: and over 84,000 healthy adults were enrolled into either colonoscopy or usual care, and the participant rate a participation rate in the colonoscopy group is pretty low, as we can see only 42. In other words, among those who are randomized to the colonoscopy group, only 42% of those really received the colonoscopy.

1:00:36

* Kresge 502 Cart: And but for the analysis, because it's a randomized trial, they still use the intended to treat design. So the results here is still based on the intended to treat analysis as we can see here, for instance, the relative risk is about 0 point 8 2, and for mortality is 0 point 9. So it's much, much weaker than the observational data, like 130.

1:01:04

* Kresge 502 Cart: So I guess the reasons why is that the case.

1:01:32

* Kresge 502 Cart: I want you, yeah, we can maybe have some discussion. That sounds good. So here, all the essential data about the trial and about the data about the results.

1:01:41

* Kresge 502 Cart: I think I had forgotten about the the fact that the the on the incident.

1:02:01

* Kresge 502 Cart: so for the sake of time we publish started a discussion any thoughts why, the results are much weaker from this trial compared to the observation data. As an epidemiologist, how to interpret the observation of universal funding is probably one of the most critical questions

1:03:57

* Kresge 502 Cart: here I list a few issues to consider.

1:04:31

* Let's start with pragmatic design.

1:04:35

* Kresge 502 Cart: Do you guys see the difference between this study design versus the traditional trial design, because in the traditional clinical trial we normally would do the consent. First, only individuals who give the consent will be randomized to the treatment of plausible group. But in this trial they actually randomize individuals first, and then collect the consent only from the treatment group.

1:04:41

* Kresge 502 Cart: Any thoughts like, why, the, in fact, is so weak.

1:05:08

* Kresge 502 Cart: Yes.

1:05:21

* parts of the observation on one. Here we are doing intention to treat so more than half of the people that were supposed to publicly.

1:05:23

* Kresge 502 Cart: they call most of the dealing actually receives. So we are underestimated. Yeah, yeah, that's definitely one object

1:05:34

* Kresge 502 Cart: potential reasons, because the low participation rate in the innovation group. Can you guys see some athletes to support from the 2 figures

1:05:43

* Kresge 502 Cart: like, let me ask first for the business speaker. Are you surprised? The better? Crossing

1:05:58

* Kresge 502 Cart: between the 2 groups, like the blue is the control group, and the red is an intervention group.

1:06:05

* Kresge 502 Cart: So they cross over

1:06:13

* Kresge 502 Cart: at about 6 years after intervention, I mean, after the start of their trial.

1:06:15

* Kresge 502 Cart: is this expected or unexpected?

1:06:23

* Hi.

1:06:35

* Kresge 502 Cart: like regularly the usual treatment? So if they already have the usual treatment. Then it comes

1:06:37

* Kresge 502 Cart: detected. There is.

1:06:48

* Kresge 502 Cart: And, for example, in the earlier ages, like in their year. Sorry

1:06:51

* Kresge 502 Cart: because we are.

1:06:58

* Kresge 502 Cart: It's mainly like a detection. But we are detecting the prevalent cancers from the population. That's why the instance is actually higher in the innovation group compared to the control group. But why? The instance gets lower in the Innovation group?

1:07:00

* Yes.

1:07:25

* Kresge 502 Cart: exactly. And also you can remove the polyps, which is a precursor addition. So I realize not all of you. So the colonoscopy does not only detect cancer or polyps, it can actually remove the lesions, and it can be both

1:07:28

* Kresge 502 Cart: considered as both preventive and also to some extent therapeutic. It can actually remove the precursation. That's why the incidence gets lower over time. So this is pretty commonly observed for conduct, space for clinical trials. But are you surprised? Let me ask it this way for mortality. Do you expect a similar crossover, or

1:07:52

* Kresge 502 Cart: you wouldn't expect

1:08:20

* to.

1:08:27

* Kresge 502 Cart: Yes, because if you're in the area, then

1:08:36

* the risk of life progressing to the cancer itself prices because

1:08:42

* Kresge 502 Cart: you gave me call it?

1:08:48

* Kresge 502 Cart: Oh, yeah.

1:08:56

* Kresge 502 Cart: yes.

1:09:09

* Kresge 502 Cart: I mean from the death certificate, you will still know, like I mean, it's likely like a son may not be diagnosed even at a death, but that's

1:09:20

* Kresge 502 Cart: unlikely, I think, in the in the.

1:09:32

* Kresge 502 Cart: in general, like

1:09:36

* Kresge 502 Cart: people who die from colon cancer like, they also probably have received a diagnosis before.

1:09:38

* Kresge 502 Cart: So the detection bias is actually normally is only observed, for instance, but not for mentality. And this is. I guess, for me this is unexpected for mentality. We wouldn't expect such crossover for mentality, and the fact that the Innovation group had a higher mortality, like, as you can see roughly like 4 to 7 years, suggest that there's something with the innovation group, right?

1:09:48

* Kresge 502 Cart: So because of the low. Again, because of the low participation rate, it is possible that individuals who are at high risk, either based on beneficially based on their perceived risk, they may be more likely to receive the colonoscopy. They may be more likely to participate, and that may lead to their higher mortality compared to their control group.

1:10:21

* Kresge 502 Cart: And that's why I think it will be very interesting to compare the risk factor information in the

1:10:48

* Kresge 502 Cart: in 2 different groups to say what exactly

1:10:58

* Kresge 502 Cart: what a group of patients of individuals are really participating in the trial, to figure out what's going on with the contribution of low participation grade.

1:11:02

* Kresge 502 Cart: So let me ask a group question. So for the incidents, that part, is it possible that

1:11:16

* Kresge 502 Cart: a participant rate is higher. In the early years since randomization

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* Kresge 502 Cart: probably invited me. The partisan

1:11:36

* Kresge 502 Cart: doesn't participate or take less of scope.

1:11:40

* Kresge 502 Cart: After many years of the migration, maybe like 5 to 10 years after resignation. So their autism rate gets decreased too. So you are seeing this is because the innovation group gets north in time

1:11:45

* Kresge 502 Cart: after a recommendation.

1:12:07

* Kresge 502 Cart: 10 rains like would change during years. Yeah, I think the 42% is average. There may be some variation over time.

1:12:10

* Kresge 502 Cart: like maybe, like in the early years there's a higher participation. And then it went down. Yeah.

1:12:34

* Kresge 502 Cart: but I wouldn't expect that's a good point, because the baseline is a recommendation. So there is left truncation people who have to be randomized, and for the innovation group it may take some time for them to receive the colonoscopy after randomization. So there is the left truncation issue.

1:12:41

* Kresge 502 Cart: And I'm also curious about the observations. Oh, so for observational study, it is just comparing individuals who receive the colonoscopy versus who did not. So it's based on that observational data. It's not like all.

1:13:10

* Kresge 502 Cart: So we won't discuss that because you can consider the observational study as comparing those who receive the innovation compared to the rest of the individuals, whereas in this clinical trial they are comparing the individuals who were randomized to intervention versus those who were randomized to to control.

1:13:35

* Kresge 502 Cart: So that's why I guess.

1:14:01

* Kresge 502 Cart: what is the trial measuring right in this study? It's measuring different things compared to the observational study.

1:14:04

* Kresge 502 Cart: Thank you. Yeah, so yeah, normally for randomized clinical trial, we are interested in efficacy. In other words, we are interested in the true effect

1:14:12

* Kresge 502 Cart: in a controlled sighting. But in this study, because of the pragmatic design, what they are measuring is actually that effectiveness rather than efficacy

1:14:25

* Kresge 502 Cart: that may also contributed to the much weaker effect.

1:14:37

* Kresge 502 Cart: Oh, you need time. Now, what do you mean by time? Like, Oh, I see. Okay, yeah. And like, it definitely can influence like. For colonoscopy. Normally, it's recommended every 10 years like after negative chronoscopy, right? Like it's possible some individuals make repeated colonoscopies. But like II don't think that's accounted for in the analysis. Yeah.

1:15:13

* Kresge 502 Cart: then, in the observational data, they just considered any chrominosphere some individuals may get one. Some may get 2 or more.

1:15:42

* Kresge 502 Cart: Yes.

1:15:54

* Kresge 502 Cart: death. Yes, I mean right to answer specific

1:15:59

* Kresge 502 Cart: I think it is. I think it is the Colorado concern, specific to death. But I can double check. Yeah, like a communication. Right? Yeah, that's good point.

1:16:06

* Kresge 502 Cart: I think it is colon cancer specific there. So this is a current screening guidelines. So because of the increase in early onset cancer screening, the starting age has been lowered to 45 from 50. It used to be 50, and now it's 45,

1:16:31

* Kresge 502 Cart: and continued until 75. And there are different options besides colonoscopy. But colonoscopy is still the most popular method in this country.

1:16:52

* Kresge 502 Cart: and there's a lot of issues with cholera to cancer screening. First one is still the sub optimal uptake and disparity. As we can see, the uptake rate varies across the States.

1:17:03

* Kresge 502 Cart: and probably, I think Massachusetts has one of the highest rates across the country, and in general the uptake has been increasing, but for Hispanics, as we can see it still lags behind other racial groups.

1:17:18

* Kresge 502 Cart: And there is also the concern about interval. Cancer, like individuals who had a negative colonoscopy, may still get colorectal cancer before their next recommended colonoscopy.

1:17:36

* Kresge 502 Cart: and we are still figuring out what is causing the info cancer, and, as I mentioned earlier, the serrated cancers are more likely to occur in the interval after negative Columbus.

1:17:51

* Kresge 502 Cart: and there is still uncertainty regarding when to start and when to stop screening, and the starting age was lowered mainly because of the rising incidence of early onset cancer. But there is a lot of concern about the overuse of screening among healthy, low risk young individuals.

1:18:05

* Kresge 502 Cart: whereas the the for the only individuals who are at high risk, they may not get the colonoscopy in a family manner. There is also the

1:18:29

* Kresge 502 Cart: concerned about the aging right as the population is aging, whether we should also extend the stop age of colonoscopy to an older age. Right now it's 75,

1:18:39

* Kresge 502 Cart: and there is a potential for personalized or precision prevention, because colonoscopy is very expensive and it is very invasive. It carries some very severe complications, so it makes sense from the population perspective to tailor the chromosome to individuals who need them most. So this is a study that we did.

1:18:53

* Kresge 502 Cart: trying to look at the risk of profiles. According to risk factors. As we can see, we considered the major risk factors for colon cancer. And we plot the age-specific colon cancer instance, we can see that if we draw some line

1:19:17

* Kresge 502 Cart: to indicate when to start a conduct based screening for the high risk individuals, they may start as early as 44 years old for older individuals and for the low risk individuals. They may not admit it until age 56, because their risk did not gather to the same level until very later in time. So that indicates the potential for personalized screening.

1:19:34

* Kresge 502 Cart: And finally, I just want to briefly talk about terra prevention. Turf prevention is about improving survivorship among patients with established cancer. And we have been studying the role of lifestyle in improving colonial cancer survivorship. As I mentioned earlier, there is an increasing number of cancer survivors

1:20:02

* Kresge 502 Cart: who are really eager to adopt lifestyle modification in order to facilitate their prognosis and treatment, but there are a lot of challenges with observational data, reverse causality conforming, and also the heterogeneity by stage and treatment, and also some exposure may become part of the clinical cause of the disease, such as weight loss. So it's really

1:20:24

* Kresge 502 Cart: difficult to study how these risk factors may influence prognosis after cancer diagnosis, and these people just summarize the factories that have been linked to colon cancer survival after diagnosis.

1:20:49

* Kresge 502 Cart: And right now, what I'm most interested in is actually coffee, because it has been showing to be beneficial across different observation studies, and the findings have been very consistent. And right now we are doing a randomized, controlled trial to test the benefit of coffee among cold patients. So, again, trying to integrate observational studies

1:21:04

* Kresge 502 Cart: with clinical trials, to better understand the risk factors

1:21:29

* Kresge 502 Cart: and to summarize colon cancer is highly preventable by screening and also by lifestyle modifications, and while screening is warranted that lifestyle factors should still be the predominant factors to consider for prevention and studies on the interplay between data and a microbiome will prove by important mechanistic and translation inside

1:21:35

* Kresge 502 Cart: in the future, and in more studies, preferably clinical trials are needed to understand the role of data lifestyle in terms of survivorship.

1:22:03

* Kresge 502 Cart: because, compared to instance, the survivorship, the innovation doesn't take that long to see an outcome among patients with colonial cancer. So we need more clinical trials to better understand the role of these risk factors

1:22:12

* Kresge 502 Cart: and to summarize. This is all the factors that we have considered in this lecture regarding their role in the natural natural history of coloreal cancer. Some of the risk factors really play a role in the early stage of cancer development. That's why there's a long latency period for other factors. They are more likely to play a role

1:22:31

* Kresge 502 Cart: in the intermediate or even in the late phase of cancer development.

1:22:56

* Kresge 502 Cart: So this is what I do. And I'm happy to answer any questions you may have feel free to email me if you are interested in studying colon cancer as I showed you in this lecture, there are still a lot of unknowns to be studied for Colonel.

1:23:03

* Kresge 502 Cart: Thank you.

1:23:21

* Any remaining thoughts or questions.

1:23:27

* Kresge 502 Cart: Yes.

1:23:36

* really. Come up on that massive. It's like, completely, I don't know.

1:23:39

* Kresge 502 Cart: Oh, I see. Okay. Oh, okay.

1:23:48

* Kresge 502 Cart: yeah, yeah, thank you for checking. Yeah, I guess not. Surprising is the infiltration of the unhealthy lifestyle across the country.

1:23:58

* Kresge 502 Cart: Thank you.

1:24:12

* Kresge 502 Cart: Great. Thank you. So much excellent.

1:24:16

* Kresge 502 Cart: What do you want us to do here?

6.

* For this 50 or 55 years later and based on his name it was called the ruse sarcoma virus that was identified and it took a time for him to be really recognized for this landmark.

7:07

* So, each year, 15% of incident cancers globally. So about 2.3 million cases are attributed to infectious causes.

7:21

* I'm gonna stop sharing for a moment and I'd love to hear from all of you. What are some of the major cancers that you think or that you've heard about are associated with an infectious cause.

7:33

* So if you've heard about are associated with an infectious cause. So if you're online, just raise your hand and infectious cause. So if you're online, just raise your hand.

7:45

* If you're in the room, raise your hand. If you're in the room, raise your hand and Colleen and Michelle, if you could just let me know.

7:50

* Okay.

7:51

* It's a little hard to see people. If they're raising their hands. So if anybody has a specific.

7:53

* Cancer that they think of as having an infectious cause.

7:58

* Sorry, was that?

8:05

* Yes, Cervical cancer.

8:06

* Shh!

8:11

* Okay.

8:19

* Cervical cancer, absolutely. And cervical cancer is an interesting cancer because HPV infection, whether it's, subtype 16 or 18, are thought to be necessary causes of cervical cancer, meaning that HBV infection is present in an estimate 100% of cervical cancers.

8:20

* It's not sufficient to cause cancer. There's other factors that help to progress it, but it certainly is an infectious ideology.

8:33

* Okay.

8:56

* Pencreatic cancer has been an interesting cancer. I think there's hypotheses, for example, there's some interesting work around H pylori infection, for example, there's some interesting work around H pylori infection in pancreatic cancer, but I wouldn't say yet that it's an established cancer with an infectious cause, but there is some interesting hypotheses.

8:57

* Right, so interestingly there's other cancers that HPV causes or a pharyngeal cancer is an example of that.

8:58

* Yeah.

9:06

* Okay.

9:15

* Anal cancer is also caused by HBV infections. And I think this has been really an important thing because I think there's some thoughts in terms of vaccination for HPV, you know, about why boys should get infected.

9:16

* Yeah. Okay.

9:20

* I think there had been a misconception that boys would not get HPV related cancers. So I think that's been an important discussion.

9:24

* Okay.

9:29

* And then yes, gastric cancers have an important ideologic cause primarily H pylori.

9:31

* So let me let me share my screen again. And again, can you see my slides here? Okay, perfect.

9:38

* Yeah, yeah, we can.

9:44

* So this is this is a slide from an article from 2,020 and the size of the circle refers to the overall burden of the number of cases of cancer globally.

9:45

* So the larger the size, the more cancers that occur globally. And then the darker green part is the the proportion of the cancer not attributable to an infectious cause and the lighter green is an estimate of the number of cases attributable to the infection.

10:00

* So again, as I mentioned with cervix nearly a hundred percent attributable to HPV.

10:19

* So gastric cancer stomach cancer about 90% of the large burden of stomach cancer that occurs globally, have an infectious ideology.

10:23

* We'll talk about liver cancer in a lot of detail. The the proportion that's attributed to infections globally is about 77%, but in different parts of the world different because of the problems of different infections that contribution plays a different role.

10:28

* Remember the estimate of puberty in a attributable fraction is a function not only the strength of the association of an exposure and cancer, but also the prevalence of that exposure in different populations.

10:49

* We'll also be looking at some of these other cancers that are more rare in the population but actually you know for example nasopharyngeal cancer, Kaposi sarcoma that have a very high infectious ideology.

10:56

* Thank you.

11:17

* And, the, as I sort of talked about with liver cancer, actually the overall proportion of cancer to trivial to infections varies considerably by the type of agent as well as the world.

11:18

* So at the very low end, probably about 4% of all cancers in Australia, New Zealand are thought to have an infectious cause, whereas in sub-Saharan Africa, percentage is as high as 32% and also what the underlying causal agent is.

11:32

* So for example in sub-Saharan Africa you can see about half of all of the infection related cancers are due to human papilloma virus, whereas in let's say eastern Asia, we have a big proportion that's due to a helicobacter pylori and stomach cancer pylori and stomach cancer as well as hepatitis B virus, pylori, and stomach cancer, as well as hepatitis B virus attributed to liver

11:44

* cancer. And you can sort of see across different parts of the world, as hepatitis B virus attributed to liver cancer.

12:12

* And you can sort of see across different parts of the world, Titus B virus attributed to liver cancer.

12:16

* And you can sort of see across different parts of the world, different distributions of the types of infectious agents leading to a proportion cancer, trivial to infection, and as well as the overall levels.

12:18

* Yeah.

12:27

* And so I've also just to say that I've. Shrunk the the people on the zoom so I can't see you so if you have a question or a comment that you wanna wake just raise your hand and Michelle and Colleen I kindly ask you to.

12:28

* Okay.

12:40

* Just let me know if someone's asking a question.

12:41

* Okay. Okay. Okay.

12:43

* I want to talk a little bit about the International Agency for Research on Cancer, which is part of the World Health Organization.

12:45

* They actually have a very formalized process by which they go through and systematically review and classify agents either to be group one which is thought to be known to be Carsonogenic to humans, then they have to be known to be carcinogenic to humans.

12:48

* Then they have 2 kind of subgroups for 2 A and 2 B, which are probably or possibly carcinogenic to humans.

13:13

* And group 3 is there's not, it's not classifiable as to its carcinogenic in a carcinogenicity and that's primarily maybe because there's not enough evidence one way or the other.

13:20

* 2.

13:49

* And then a group 4, which is probably not carcinogenic to humans. And so in this systematic review, there's a hundred 22 different agents based and this is based both on experimental studies, animal studies, and epidemiologic studies where the evidence is felt to be sufficient to classify to carcin to humans.

13:50

* Okay.

13:53

* And if you go to this link at the bottom of the page, it gives you more information about IRCs classification process, and how the, and what specific agents are classified into these different groups.

13:57

* And I'm just saying this because if we look at those 122 agents, a number of the agents are actually infections.

14:10

* And this graph here just looks at the number of infections causes that are associated with at least 5 different cancer sites.

14:20

* So HIV infections associated with as a group one carcinogen for 5 different malignancies.

14:31

* Just as an example, alcohols associated with 7 tobacco 17, but we have HPV infection that's HPV.

14:38

* Yeah.

14:45

* 17, sorry, HPV 16 does it known to be associated with at least 7 different cancer sites.

14:47

* Yes.

14:56

* So as I mentioned, Epstein bar virus is, was first discovered because of its association with burkets, lymphoma, but it's now been shown to have group one evidence that's associated with Don Hodges's symphoma.

14:57

* Hi, to, as well as nasopharyngeal cancer. It's interesting if you took blood on a group of adults including in the United States about 90% of individuals have been infected with Epstein-barr virus during their lifetime.

15:11

* Therefore, is this observation surprising to you and is it compatible? Compatible with the Epstein-barr virus being a causal cancer risk factor for these cancers.

15:32

* And why or why not? I'm gonna stop sharing for a moment. We're gonna do our first breakout session.

15:43

* Take a couple of minutes to think about. So we have a causal agent where 90% of the population is exposed to that agent.

15:50

* It's

16:00

* And it seems to be associated with these cancers that are not particularly common. So does how does that make you feel about Epstein bar virus as a causal agent for cancers.

16:01

* Take a about a couple minutes, go to your breakout rooms. And then we'll come back together.

16:12

* Okay.

16:18

* I don't know, Colleen and Michelle are the breakout rooms open.

16:19

* I'm gonna open them right now.

16:22

* Thank you.

16:26

* Okay, perfect. Okay, so you'll see on the bar on the bottom it says breakout rooms.

16:27

* You click on that and you just go into one of the breakout rooms.

16:32

* And you guys, yeah, exactly.

16:41

* And you guys will talk here. Well, me at the room so that's not too bad.

16:42

* Okay, perfect. That's sounds great. So we'll take 2 min.

16:46

* So I just send a note to the room, the breakout rooms that will come back together.

18:05

* In about 30 s.

18:06

* Okay, okay, that's no problem. That's great. Excellent.

18:28

* Laura, I just closed the room, so it's going to take 60 s for everyone to reach.

18:29

* Perfect. Great.

19:22

* Yeah.

19:23

* So I'd love to hear some of the discussions. So I'm gonna first, kind of put it to the room.

19:28

* And then we might need, People just to, Michelle and calling to. Just so we can hear it.

19:36

* She's No. Yeah.

19:37

* But any thoughts from the the Kreski FIVO 2 on that question?

19:43

* One of the things that we talked about was the causal pie and how it could be a component. Of a particular causal pi and there's other factors, variables that when put together.

19:58

* Cause All the cancer but or not it's not sufficient alone to cause the cancer. That's why you have a bunch of other variables that have been found to be personal kicking, there's just still a lot of.

20:14

* Investigations that can be. Done to better understand the relationship between the and other barriers.

20:28

* Right, no, that's a great point. And I think we see it with other cancers that have infectious causes that the infection alone isn't.

20:35

* Okay.

20:51

* You sufficient but there there might be like as I mentioned in with Berkenson from there seems potentially synergy with malarial infection, maybe there's, you know, other things like diet or smoking that also might interact.

20:52

* Okay.

20:58

* So there may be other host components that are required to be present in order for EBV to work.

20:59

* So that's that's a great answer. What I'm gonna open it up to and ask anybody on zoom some of the discussions you had anything else to add to that conversation

21:04

* Feel free just to say something if you want to. Yeah, go ahead

21:18

* Yeah.

21:24

* I can add from my perspective that's TBV as you said is sufficient, but it's required but not sufficient for the endemic form.

21:25

* Okay.

21:31

* Yeah.

21:33

* Yeah.

21:40

* Okay.

21:43

* Of Berkeley in form as you discuss it. It's mainly we see it in kids in Africa that present with large stomach so it's also focuses on a specific population of patients.

21:44

* Hmm.

21:47

* Okay.

21:49

* Yeah.

21:52

* Okay.

22:06

* I mean it's mainly in children and and not adults. I mean this type that is EBV and malaria associated so I guess it's a it's it's a composition of a lot of components and EBV plays their major role in the oncogenesis or the development of cancer, but is Not sufficient and and and Well, at least that's my perspective on the.

22:07

* Yeah, so other kind of host factors in this population. Of children that might make them more vulnerable to an infection like each EBV, together with or without malaria.

22:12

* Yeah

22:22

* Yeah. What about what about the virus itself or did was any of the conversations that you had about other aspects of the virus, do you think?

22:23

* Okay.

22:32

* Like is it just the virus being there or not?

22:33

* Okay.

22:41

* Well, maybe what I'm gonna share my screen again and I'm gonna show you some data.

22:42

* And maybe this maybe tell me if this gives you any thoughts. So this this was a study that was done in Sweden in Denmark.

22:49

* Looking at Epstein by bar virus and the risk of Hutchins and Foma so Epstein-barr virus also is a cause for mononucleosis.

22:57

* Okay.

23:08

* Okay. Okay.

23:17

* And so this particular study looked at the association between years since infectious mononucleosis as a measure of timing in a person's life of Epstein bar virus and then the risk of Hodgkins and Foma and sort of the timing of it and so the blue lines represent the cases of where the tumor cells had presence of Epstein bar virus and the red looks at Epstein bar virus

23:18

* Yeah. Okay.

23:49

* negative and essentially what you can see here is that there's a sort of a distribution of and on the y-axis is the relative risk of lymphoma.

23:50

* Okay.

23:55

* Okay.

24:08

* And you can see in the first 4 years after mononucleosis, the risk of Hutchins and Foma goes up substantially and then starts to decrease although even 10 years out you're seeing about a 4 fold greater risk.

24:09

* Yeah.

24:12

* None of them are associated with the virus of the timing of infection is important and I'll bring up another example with cervical cancer talking about viral load as well.

24:14

* So it may not be just the virus that it's there or not, but it may be the age at which someone's exposed.

24:30

* It might be the amount of viral load that they're exposed to, etc, and all of these things may be really explaining why even though the prevalence of EBB is so high in addition to host factors that it may be other factors associated with the virus itself that may be related to.

24:33

* Okay.

24:57

* Yes.

25:02

* Yeah.

25:14

* Whether or not someone develops cancer and I think what's interesting here again we talked about latency a couple of lectures ago what's interesting here is you can see this is a relatively short latency right between when someone is exposed to Epstein bar virus again through demonstration of mono nucleosis and the tide the peak of time in which someone's developing cancer.

25:15

* Okay.

25:22

* It's a pretty short window as opposed to when Dr. Song talked about colorectal cancer and smoking where you were seeing really about a 20 where 20 year latency between smoking initiation and development of colorectal cancer.

25:23

* Okay.

25:35

* So the next 2 slides really are not meant for you to memorize, but really to provide an overview of synopsis of all of the viruses and infections.

25:36

* That are felt to be group one agents. So again, according to the international agency for research on cancer, these infections agents are thought to be cancer associated infections.

25:47

* And the the first column are the cancers for which there's sufficient evidence. The next column is where there's more limited evidence.

25:54

* The next column is where there's more limited evidence, but there's more limited evidence, but there's, you know, it's where there's more limited evidence, but there's, you know, it's interesting hypothesis that may be associated.

26:09

* So just as for example, we already talked about Epstein-barr virus. We'll talk a lot about hepatitis B and C viruses in their relation to different types of primary liver cancer.

26:15

* HIV infection. There's very good evidence. Of that HIV associated cancers not only Kaposi sarcoma, but lymphoma's and as well as cancers of the cervix, and is, etc.

26:24

* Bye.

26:41

* We talked a little bit about HPV related malignancies. And then we're gonna talk a little bit about, I'll look back to Pylori and some really interesting evidence around liver floops.

26:42

* The one that we won't talk about is something which is felt to be a subset. Of bladder cancers in a specific part of the world.

26:51

* That are associated with a schistoma infection. And again, I'm sorry, I can't see people now in the class or on Zoom.

26:56

* Yeah.

27:12

* So if you have a question. Raise your virtual hand or your hand in class and Michelle and Colleen will just let me know if you have a question.

27:13

* Oh

27:18

* So an important question. You might ask is, well, how could infectious agents cause cancer?

27:19

* Thank you.

27:27

* And there's thought to be a number of ways in which this might happen. And, and I, I want to bring in the concept that we talked about a couple of classes ago about some factors.

27:28

* Okay.

27:34

* That are initiators of a cancer. So they're those these are the things that can actually go in and do damage to DNA early on.

27:35

* Okay.

27:46

* And then there's things that promote the cancer. Promoters and these are things that may take a single cell or subset of cells and allow those cells to grow.

27:47

* Okay.

27:56

* In formalize into an actual tumor. So for viruses, some viruses are able to integrate their DNA into, human cell DNA and lead to direct damage and mutations themselves.

27:57

* Okay.

28:17

* Yeah.

28:20

* So these are the types of ways that were things that we call initiators. And then there's additionally some of these same infections or viruses that, lead to sort of this chronic level of inflammation.

28:21

* Sure.

28:32

* So if you think about inflammation as sort of like fueling these subset of damaged cells to grow and and proliferate and and that may also lead to cancer growth.

28:33

* And then in addition, some viruses, for example, can actually lead to immunosuppression.

28:37

* And so it's through the immunosuppression that's allowing other agents maybe happening in the host to be more damaging than others.

28:44

* So they really are multiple ways in which infections can actually lead to cancer development.

28:51

* And I think in an example of, immunosuppression and its important role in cancer development.

28:58

* This comes from a. Meta-analysis of studies that looked at what is the association between different infections and the risk of cancer in different in 2 different types of immunosuppress population.

29:06

* So the first immuno press immunosuppress population are each of the positive individuals. The second are patients who are undergoing organ transplant.

29:19

* We're in order to avoid rejection of a donor organ you you suppress the immune system.

29:24

* Hello.

29:41

* So these are 2 groups of individuals that have high immunosuppression. And so these are relative risk measures looking at the association for example between HPV and infection and these different cancers in these 2 groups of immunosuppressing individuals.

29:42

* And I think what may really jump out to you is what you can see for many of these infections, the relative risk of say 10 or even 50 full greater risk of these cancers in the presence of HPV.

29:58

* Compared to the absence. And then when we look at other types of infection related cancer, so for example, Epstein bar virus, human, herpes virus 8.

30:06

* The hepatitis viruses and liver cancer, you can just see the fact that immunosuppression has, you know, you can see here over a hundred full greater risk of these cancers in the presence of immunosuppression.

30:22

* So, so again, thinking about the role that the host might be playing interacting with infectious agents in increasing the risk of cancer occurring.

30:35

* Thank you.

30:43

* Oh, so, what's been interesting and I along this idea of immunosuppression that with the advent of antiretroviral therapies because these are reducing immunosuppression in HIV positive individuals.

30:46

* There's been a reduction in the incidence of AIDS to find cancers in the HIV positive population.

31:01

* Would spend an important observation.

31:04

* Yeah.

31:11

* So, you know, a lot of time, so one of the things I mentioned, in talking about Epstein bar virus is not only do you get the infection or not but what is the age at which someone's infected.

31:12

* And that's going to be really important for a range of different infections because what it allows depending on the age at which somebody is infected, there might be maternal antibodies, there may be other windows of greater susceptibility, so some infections are more likely to be cleared.

31:25

* Okay.

31:45

* Depending or or on the flip side, more likely to become a chronic affection depending on the age at which somebody is exposed to the infection.

31:46

* So 2 different proxies for agent exposure to infection, right? Because it's hard to know some some infections are silent, right?

31:49

* You might be exposed to a specific infection and there's no clinical symptoms in that infection. So you actually oftentimes may not know when someone's exposed to an infection.

31:59

* So we use SIP ship size and birth order. As proxies. So I wanna I'm gonna stop sharing for a second.

32:12

* Okay.

32:18

* SIP ship sizes is just the number of siblings in your family. And birth order is where you are.

32:20

* So if let's say there's 3 kids in your family and you're the the middle child you're this your birth order is 2 if you were the first born your birth orders one and if your third your birth order 3 and it and your sib ship size would be 3 So thinking about the probability in the age of earlier infection.

32:24

* What do you think if with a greater number of siblings you have or where you are with a birth order, how might that impact your age at a infection to things that are commonly, that kids are commonly exposed to.

32:47

* Yeah.

33:05

* Maybe let's top up with subship size. Do you think that if you have. 3 siblings living in your house is your probability of getting exposed to an infectious agent greater or less?

33:06

* When you're a kid. Higher, right, exactly. So SIP ship size has been one proxy for just the probability of infection to childhood infections as well as the age of which are infection.

33:15

* Now what about birth order? Do you think? How might that. Play out.

33:28

* Do you think? If you're the first born in your house, do you think you're gonna get be exposed later or earlier to infections compared to say your younger siblings.

33:35

* Later. Right, exactly, because, you know, now kids often will go to daycare so maybe this isn't as translatable but when many times when kids weren't getting exposed until they went to say kindergarten, they weren't getting their first exposure to infections really until then, whereas the younger children, they were getting it smooth from their older siblings coming over.

33:49

* So, so we can use SIP ship size and birth order as proxies for age and infection as well as the overall probability of infection.

34:11

* So there was a study that was done on birth order and citizenship size in relation to the risk of nasopharyngeal cancer.

34:17

* So using the National Health Registers in Sweden, they did a nationwide study, from 1961 to 2,009 and they did sort of a nested case control study or incident density sampling.

34:23

* They had 400 and sorry 251 incident cases of n nasopharyngeal cancer.

34:43

* In this population and then they matched on sex and birth year using density incidents density sampling for 1,255 controls and then they had information on the total number of siblings.

34:49

* Listen, Yeah.

34:50

* As well as the number of older siblings. So what does this data tell you? So this is on the left panel is looking at this.

35:04

* You're between the total number of siblings you had and I'm sorry this is the risk of mono nucleosis.

35:14

* First and then this is looking at the risk of nasopharyngeal cancer. So let's look at the risk of mononucleases first.

35:20

* So this is was part of the say, what did this tell you? About age of exposure to Epstein bar virus.

35:27

* And the risk of mononucleosis. Again, I can't see you. So just speak out or.

35:36

* For Michelle and. Just tell me if somebody is raising their hands.

35:42

* Oh

35:48

* Is it earlier or later exposure to Epstein bar virus that is going to be a more of a risk for mononucleosis?

35:49

* So looking at the PIN on the right, if you have 3 older siblings. Your risk of mononucleosis.

36:05

* Was about 24% lower compared to those without any older siblings.

36:14

* 30.

36:27

* Yeah.

36:30

* Earlier right exactly so the earlier you're exposed to Epstein bar virus the, the, greater the risk of, mononucleosis was.

36:31

* Okay.

36:40

* Now what about Bernasopharyngeal cancer? What do you see? Maybe the associations are quite as strong, but what do you see here?

36:41

* Something different, right?

36:52

* So here it looks like. Whereas earlier exposure to Epstein bar seems to be protective against developing money and nucleosis, it seems actually to be associated with an increased risk of nasopharyngeal cancer.

36:56

* Does that make sense?

37:10

* So the timing of the infection is is quite important.

37:18

* Cool.

37:23

* Alright, so I wanted to this was one of the articles that was the recommended reading for class today and this gets a little bit more about details of the infectious agents itself.

37:24

* Yeah.

37:44

* So this is a study that was done in really leveraging a unique cohort of women who underwent, pap smear screening, in Uppsala, Sweden.

37:45

* They had stored 730,000 pap smear specimens from 146,000 women between 1,969 and 1,995 these were just stored in the pathology lab and they were kind of available, you know, for clinical and epidemiological studies.

37:49

* Yeah.

38:16

* And so, this study was done by Hanzo Lafadami and his team, where they linked the pap smears with information are in the Swedish cancer registry to look at 478 cervical cancer cases.

38:17

* Okay.

38:31

* 608 age match controls from this cohort of women. And then this is looking at, a.

38:32

* Count a viral load. So essentially here, The higher the number. The greater the viral load.

38:38

* And so then this is looking at actually I apologize this is wrong so the lower sorry the lower the viral count.

38:51

* The higher the viral count. The lower that this this CT number is. So going from left to right the higher.

38:59

* Viral load is associated with a lower CT count here. And then this is looking at the association between viral load and the relative risk or odds ratio for cervical cancer.

39:09

* The first line with the open circle is one year after the pap's mirror, 4 years after the pap smear and then 7 years after the Pap.

39:22

* So first in terms of viral load based on this figure. Does viral load of HPV 16 make a difference for the risk of cervical cancer?

39:31

* Yes or no?

39:45

* Do you see a different association between higher and lower viral load? And the odds of.

39:49

* Cervical cancer in this dataset.

39:58

* 2. Someone put yes in the chat.

40:01

* Yes, exactly. And so it's pretty striking actually. So for those with the lowest, viral load, you can see the association between HPV 16 and cervical cancer was probably an odds ratio of about 4.

40:07

* Yeah.

40:38

* And then when you look at the higher spiral titers. You can see that the relative risk is dramatically increased so that if with presence of HPV 16 and a high viral load the odds ratio is about 50 And then, so just you can see these 3 different time points between when they, PAP, was taking and the risk of cervical cancer.

40:39

* So now I'm going to ask a question. How do you interpret this in terms of when cancers how cancer screening and early detection you know If you have a detection of HPV, 16 viral load.

40:45

* Present in terms of. Identifying cancers earlier through earlier screening earlier detection. How might you take this information?

41:02

* Like, do you think you need to test somebody every year? Could you wait, for example, 4 years?

41:14

* N be safe, what about 7 years?

41:20

* Yes. 4 years. Yes.

41:28

* 4 years, exactly, right? You can sort of see it looks like. You can probably fairly safely wait.

41:31

* 4 years, although of course, you know, maybe if you're in this highest group, you'd want to do more active surveillance of this population anyways.

41:41

* But right, exactly. So in terms of screening, you can sort of see this difference between what in 4 years versus 7 years in terms of the incidence of cervical cancer.

41:49

* So again, just to read it the message, it's not just whether HPV 16 is present or not, but also the viral load is really an important predictor of future cervical cancer risk.

41:59

* Okay, so I'm gonna stop sharing for a moment and I want to ask the question, are infection related cancers preventable?

42:13

* And if so, how? So just in what we've talked about so far. How could we prevent in of the infectious related cancers we've talked about?

42:21

* How could we? Think about prevention or some of the other cases we haven't talked about. Is first of all is prevention possible.

42:35

* Thank you.

42:47

* Vaccinations perhaps.

42:52

* That's vaccinations, exactly, right, exactly. So for cervical cancer, we have vaccination.

42:55

* Yeah.

43:05

* We haven't talked about it yet, but for hepatitis B virus, which is a major cause of liver cancer, we also now have vaccination which recommended at least in the United States as part of childhood vaccinations.

43:06

* How else? What about, what else for cervical cancer? Can be used for prevention.

43:14

* Hmm.

43:24

* What do we use for early detection to actually prevent the cancer from being? From from happening.

43:30

* It's great.

43:41

* Right, screen. Yeah, Pap users, exactly. So we do screening, right? And the hope with Pap smears is not only will we detect cervical cancer earlier, but will actually detect the pre malignant condition earlier.

43:42

* And remove it before cancer can even occur. So that's another way we can prevent infection related cancers.

43:46

* No.

44:04

* What about, oh, sorry, was there somebody have a comment? In the room. What about something like, what do you know about H pylori or other kind of infections?

44:05

* We, we can treat the infection. Right? We can identify and treat the infection. Yeah, and Dusky be interesting to think about, certain types of Again, what you wanting to identify.

44:15

* Cancers before they become cancer. So identifying those pre malignant lesions. But there's certain types of infections that we can prevent.

44:27

* Okay.

44:39

* I think stomach cancer we've seen dramatic decreases in the United States because of of hygiene has really dropped dramatically in the United States and in Western countries, the incidence of H.

44:40

* Pylori and therefore the incidence of gastric cancer. So there's a number of ways in which we can think about cancer prevention, focused on infections in cancer.

44:52

* And we'll talk a little bit more in some more examples when we get into liver cancer.

45:01

* Hi, I'm going to have a question. Just on the previous slide, the HPB, 16 barrel mode.

45:06

* Yeah.

45:15

* I was wondering, is it showing that this 7 year gap, I guess, in getting a perhaps near is associated with, oh, lower dress but cancer.

45:16

* Yeah, so basically, yeah, exactly. I think what you're the the way this is study with design was they they had you know, all these pap smears from women who were cancer free when the pap smear was taken.

45:28

* Okay.

45:43

* And then the question they asked was, what was the association with cervical cancers that occurred in the first year?

45:44

* In the first 4 years and then not until 7 years later. So it was trying to get at a little bit about.

45:50

* You know, is there sort of an immediate in terms of early detection and immediate increase in the odds of cervical cancer.

45:58

* So you would want to do if you saw somebody had high viral load, you'd want to keep screening them.

46:06

* Very, very regularly. Or, is, is it a slower latency and therefore you, you might be able to, in terms of early detection you might not need to be doing looking every year so I think it was I don't know if it translate directly to early detection because as I said, I think if somebody had a really high HPV 16 viral load, you'd want to have them come in

46:12

* and screen more regularly. But I think what this is getting at a little bit is that how quickly cervical cancer might develop in someone who has a high viral load.

46:38

* Yeah. Yeah. Yeah. One more question in the chat.

46:51

* Did, did that clarify the question or your question? Okay, great. Okay. Hmm.

46:52

* Someone asked, what about EPV? Are there any preventable ways?

46:59

* Oh, that's a great question. So you know, with EBV, as I mentioned, you know, ultimately about 90% of us are going to have serologic evidence that we had prior infection.

47:06

* So, you know, The question really is maybe not if we're going to prevent it altogether, but can we prevent?

47:20

* The the viral load or the age at which someone's infected and it's complicated right because

47:31

* Okay.

47:41

* The association between EBV. And mononucleosis. Or EVV and Burke's lymphoma made different.

47:42

* Okay.

47:51

* So EBV I think is a little more complicated. I don't believe that there's a vaccination.

47:52

* Epstein by virus, right? No, there's not. I don't know if someone has tried to develop one or not, but I guess that could be a strategy.

47:56

* Potentially that there's a vaccination, but currently, and I don't believe there's treatment either.

48:01

* Okay. Any other questions?

48:15

* Okay, great. So, now we're gonna go into, to liver cancer.

48:21

* And so the liver is really an essential organ that plays a number of roles from detoxification, metabolism.

48:26

* It says it stores glucogen. And as a result, You know, it's exposed.

48:34

* Blood blows through the liver and as a result it can be exposed to many different types of toxins, environmental contaminants, dietary factors, etc.

48:45

* As well as viral infections. And then as a result, similarly, it can be actually a common side of metastasis because of the blood flowing through the liver.

48:55

* And so, you know, on our first lecture we talked about different cancers when they do leave the original organ.

49:04

* They metastasize to different organs. When they do leave the original organ, they metastasize to different organs.

49:13

* Well, livers a come in sight, metastasize for breast cancer, and metastasize for breast cancer, metastasized for breast cancer, colon cancer, and lung cancer, colon cancer, and lung cancer, and lung cancer.

49:16

* This is not what we mean when we're talking about primary liver cancer. So I really try to use the word primary liver cancer.

49:21

* So I really try to use the word primary liver cancer. So I really try to use the word primary liver cancer.

49:26

* So I really try to use the word primary liver cancer instead of just liver cancer because it because liver is a common side of metastasis.

49:27

* There's a number of histologic type the most common of the histologic types is hepatitis cellular carcinoma.

49:28

* I'm also going to be talking about collagenio carcinoma which occurs in the bile ducts of the liver, whereas, hepat a cellular carcinoma is cancers that are arising in the hepatocytes.

49:40

* So I'm going to, Click on this link here and can can you see now the IRC website?

49:53

* Yes.

50:03

* Okay, perfect. Yeah, so I just wanted to kind of, I thought it'd be nice to kind of go through a little bit using this because I think you'll be using it for your descriptive epidemiology.

50:04

* But this is looking at the overall incidence of primary liver cancer across the world, incidence of, primary liver cancer across the world for both.

50:13

* Oh sorry, this is for all cancers. Let me sorry. Let me let me put it for liver cancer specifically.

50:24

* So this is for liver and intra hepatic bild ducks. This is not metastatic liver cancer.

50:28

* Okay.

50:41

* This is cancers that are primary to the liver. And so what you can see is when we look at both sexes together and this is data for 2022 we have different parts of the world with a higher burden, particularly you can see in Mongolia the, different parts of the world with a higher burden, particularly, you can see, in Mongolia, the, incidence is

50:42

* 96.1, per 100,000 in the United States. Instead, it's, it's 6.8 per 100,000.

50:58

* Okay. Okay.

50:59

* So you can see there's countries with really high incidents and then other areas for example Brazil with much lower incidents.

51:03

* So I wanted to show that we can also compare. Different populations so here we can compare different countries together across a range of different cancers.

51:11

* Etc. so i just wanted to kind of I like here if we go back here if we look at what the incidence of.

51:27

* Cool.

51:36

* Liver cancer is. Among. So this is both. Genders if we look at men.

51:37

* No.

51:45

* Okay.

51:52

* Kind of very similar patterns and if we look at women, I think the only difference is that across the board the incidence is much lower in women than it is in that.

51:53

* Oh.

51:58

* And then if we look at moreality, the countries are fairly similar as well. Someone to switch back to this slide here.

51:59

* Good.

52:04

* Yes.

52:09

* Can you see the slide again? Okay, perfect. So each year globally it's a major cause of cancer.

52:10

* There's about 865,000 in cases of primary liver cancer and 758,000 cancer deaths that occur.

52:11

* And sorry, I'm just the. Air conditioner just popped down a little bit. Open the store so it turns off.

52:24

* In 2022. All right, so this is a figure looking at on the left in blue are the incidents rate per 100,000 individuals and on the right are the mortality rates and this is looking at different continents.

52:31

* What does this figure tell you in terms of the ratio of incidence to mortality?

52:47

* They're proportional. Yeah. Their first question.

53:01

* Sorry, couldn't hear with the, They're proportional. So what does that mean in terms of is this a highly fatal cancer?

53:03

* Would you say is that do you think the fatality is high?

53:14

* Good morning.

53:19

* There's a lot of nodding around.

53:22

* Was that sorry? Yeah, a lot of nodding exactly. Yes. I think somebody in the chat said.

53:23

* Yes, yep, exactly, right. So that fatality is quite high. And as a result, and the incidence is moderate so the prevalence of people living with liver cancer is fairly low actually.

53:29

* And so this is data from the United States that we looked at earlier. Each year it's about 41,000 new cases a primary liver cancer 29,000 deaths estimated in 2,023.

53:44

* When you look at five-year survival and when Colleen and Michelle give a lecture later. They're gonna talk about different concepts in survival.

53:56

* They'll talk about what relative survival is. Essentially it's fairly low. So 5 years out, about 20% of patient diagnosed with liver cancer, only 20% will be alive.

54:05

* So this, can you, can you see my arrow by any chance? No. Yes, you can.

54:16

* Yeah.

54:19

* Alright, perfect. So there was an interesting over time sort of somewhat decline. And this is looking at death rates among men and then since 1,990 there's been an alarming increase in mortality rates from liver, primary liver cancer over time.

54:20

* Again, not metastatic diseases, primary liver cancer. And we're seeing it also in women as well.

54:39

* Okay.

54:49

* So it's an alarming trend given how fatal this cancer is. Oh, it affects in the United States people differently.

54:50

* You can really see the dramatic difference in the incidence rate per 100,000 between men and women and then there's groups of individuals with very high risk.

54:52

* So for example in American Indian and Alaska Native populations, you have very high rates also in Hispanic populations.

55:05

* There's also certain Asian and Pacific Islander populations, which we'll talk about in a moment, that are very high risk as well as black non-Hispanic individuals.

55:13

* Yeah.

55:25

* So, 2 of the major infection related causes of primary liver cancer are hepatitis B and hepatitis C infection.

55:26

* Okay.

55:31

* Hepatitis B infection, really is a different type of virus than hepatitis C, hepatitis B is considered to be what's called a DNA virus, which means the viral DNA can actually directly integrate into human DNA and as I talked about earlier in this lecture, it can actually lead to directly to damage.

55:32

* Okay.

56:06

* It also can lead to inflammation along the way if chronic infection results. And this is important to think about hepatitis B we call almost like a perfect carcinogen because it's both in initiator and a promoter.

56:07

* Smoking is thought to be that way too, that it both can initiate lung cancers to happen as well as promote it through inflammation.

56:15

* Hepatitis C and said is considered to be, it's a virus DNA, it doesn't integrate into the DNA, so it's not thought to be a promoter DNA, so it's not thought to be a promoter, but it's certainly concrete with a chronic infection a lot of inflammation, but it certainly can create with a chronic infection a lot of inflammation that

56:22

* ultimately can lead the cancer to reform. And I'm talking about chronic infection, which is really an important concept with hepatitis B and C.

56:39

* Because most people with hepatitis B will actually clear the infection if they're exposed.

56:43

* And as only if they become chronic carriers of hepatitis B or C that they will be at risk for developing primary liver cancer.

56:55

* And so what you can see from hepatitis B infection that of adults who are exposed to hepatitis B, 95% of those individuals will clear the infection and not become chronic carriers.

57:04

* Whereas for newborns if they're born to moms that are carriers of hepatitis B, 90% of them will become chronic carriers.

57:17

* So again, thinking about prevention. This is really an important thing in terms of prevention of transmission of hepatitis B infection to babies.

57:23

* In contrast, what you can see for hepatitis C, that a large proportion of individuals who are exposed to hepatitis C infection will become chronically infected.

57:40

* So that's a really important factor in terms of the future risk of liver cancer. Primary liver cancer as well as other types of infections.

57:48

* I'm sorry, other types of liver diseases. So hepatitis B was the first of the virus that was found to be associated with primary liver cancer.

58:03

* It preferentially infects hepatitis. Which are the cells that lead to hepatitis cellular carcinoma, which is the primary subtype of primary liver cancer.

58:14

* As I mentioned, it integrates into the host DNA. And there's this is what the virus looks like.

58:24

* And the reason I'm showing this is if you look here on the lower right, the hepatitis B surface antigen.

58:27

* It's an important biomarker because it's a measure of acute or chronic infection and it's the biomarker that's most often used in epidemiologic studies to look at the association between hepatitis B and risk a primary liver cancer.

58:38

* So it unfortunately over 300,000 individuals around the world have chronic hepatitis B infection.

58:51

* There's a lot of variability in around the world as I mentioned, a high prevalence of chronicity in infants who are born to hepatitis B.

59:05

* Infected mothers. So given and compared to 10% who are teenagers when they're first exposed, how do you think then let's talk about birth order remember so the Later you are.

59:11

* Born, the greater the likelihood you're exposed earlier. To an infection. What do you think the association is between birth, order, and primary liver cancer?

59:30

* Do you think it's a positive association or an inverse association or no association?

59:43

* So.

59:55

* So the higher the birth order, the earlier you're exposed.

59:56

* Okay.

1:00:00

* And it looks like the earlier you're exposed, the more like you are to become a chronic carrier.

1:00:02

* Okay.

1:00:13

* Well, it's sort of so the earlier you're exposed to happen times be the more likely you are to become a chronic B, the more likely you are to become a chronic carrier of hepatitis B infection.

1:00:17

* Therefore, the greater your risk of hepatitis B infection, therefore the greater your risk is going to be a primary, therefore the greater your risk is going to be a primary liver cancer in the future.

1:00:20

* Okay. Hello. There's a

1:00:30

* One of, oh, sure. There's a comment. Yep. Oh, yep.

1:00:31

* Yeah.

1:00:40

* Hey, Lori, I just have a question about, when you say chronic areas, does that mean that they're is that having to do with like the DNA?

1:00:41

* Getting us affected by the virus or Like, I think I'm just like overthinking. Yeah.

1:00:48

* Yeah, no, no, no, I think it's a really good question. I think what it, it kind of means is that your body is able to just get rid of the virus.

1:00:55

* Right.

1:01:04

* Whereas with a chronic carrier, you're not getting rid of the virus. So the virus is going to continue to be able to do damage to DNA and it's going to be able to continue to lead to inflammation.

1:01:05

* Hmm.

1:01:16

* Whereas like, you know, like just if you think of like a common cold Most of the time you get exposed to a virus, a cold virus, and then you're able to just get clear it from your body and that virus is no longer.

1:01:17

* Part of your body. So right, the chronic. Carriers are more likely where it's in integrating into your DNA and remaining part of your body and leading to that chronic.

1:01:32

* Inflammation and doing more damage.

1:01:44

* I see. So is it like if you have chronic inflammation then that is an indicator that It is like chronic case of hepatitis.

1:01:46

* Yeah, that's a great question. So there's a lot of different causes of.

1:01:55

* Hmm, I see.

1:02:16

* Of leading, you mean in doing liver damage, etc, and seeing the inflammation in the liver, but there's many things that can cause it so it doesn't necessarily mean you have hepatitis B, you would really have to do a blood test to show that you positive for hepatitis B and you do it for that hepatitis B surface antigen.

1:02:17

* Oh.

1:02:22

* That's going to be the best marker to show that you're chronic carrier of infection.

1:02:23

* Thank you.

1:02:25

* Gotcha. Thank you.

1:02:26

* And I'll talk, I'll show you kind of this model that synthesizes how all the risk factors might be playing a role in, in the development of primary liver cancer.

1:02:28

* So one of the really early studies that really helped us establish, hepatitis B virus being associated with, hepaticellular carcinoma was a study done by Demetrius Jacobis who was a former chair of epidemiology at the Harvard School of Public Health.

1:02:33

* He did this hospital base case control study in Greece. He recruited at 80 patients that had been diagnosed with the padocalio carcinoma.

1:02:50

* He also recruited 40 patients who had metastatic liver cancer. And then EDH sex match controls and then he took blood specimens from all of these individuals to measure different hepatitis B biomarkers.

1:03:05

* So I guess why do you think he included? Both primary and metastatic. Liver cancer. What as well as controls.

1:03:21

* If you wanted to show that hepatitis B virus infection was a causal agent. For bimary, hepatocalial cursor.

1:03:31

* Why did he include metastatic?

1:03:40

* Yeah.

1:03:42

* Liver cancer do you think in this hospital based case control design?

1:03:43

* What did we do a quick breakout? Is it is it hard to set up?

1:03:56

* No, I can do it.

1:04:00

* Alright, while we take a quick break out and just talk for a minute, let's soon like, 90 s, for this and talk about what is the importance, in this hospital-based Case control study.

1:04:01

* That he thought to include metastatic liver cancer in addition to hospital-based controls in the study.

1:04:16

* Alright, so go ahead and join a breakout room or in class turn to your neighbor and let's have a 90 s discussion.

1:04:27

* Should we, if we close out the rooms now, Michelle, do we, that gives them a minute.

1:05:27

* Yeah, I can do that.

1:05:34

* Okay. I, I can do it too.

1:05:36

* Perfect.

1:05:41

* Good morning.

1:06:36

* Okay, is everybody back? That's it. Okay, perfect.

1:06:37

* Okay, now everyone should be back.

1:06:40

* Oh, perfect. Fantastic. That's great. Excellent.

1:06:41

* Yeah.

1:06:48

* So let's, I'm gonna turn to our, colleagues on Zoom to ask first, what were some of your discussions about why do you think Dr.

1:06:49

* Chakopoulos included. Metastatic liver cancer as well as hospital base controls. In this study.

1:06:54

* Any thoughts any, what were some of your discussions?

1:07:11

* We weren't really sure that. In common fashion, I'll shout out one of my.

1:07:18

* Yeah.

1:07:25

* Thank you. Perfect, perfect.

1:07:26

* My breakout roommates. Meeting said that, it could just be that they're associated.

1:07:27

* Okay.

1:07:29

* With both.

1:07:31

* Oh, that's interesting, right. So, you know, it maybe there's some way in which hepatitis.

1:07:33

* B infection could damage the liver, so making it more vulnerable. That's an interesting hypothesis.

1:07:41

* So actually, so in maybe I'll turn to the room then any thoughts from the room about why They were included.

1:07:48

* Okay.

1:07:56

* Okay.

1:08:00

* Any thoughts?

1:08:05

* Well, remember, this was a hospital based case control study and the controls. You know, you kind of always worry a little bit about selection bias.

1:08:09

* Because the controls were taken from the same hospitals, so might have had other conditions. And so actually, The hypothesis was that hepatitis B, virus should not be associated with metastatic.

1:08:23

* Yeah.

1:08:42

* But it should be with. The other cancer if there is an association. So it's almost like an additional.

1:08:43

* Second type of negative control with this idea that the the selection forces for going to the hospital for primary liver cancer might be similar for metastatic. Liver cancer.

1:08:48

* So that was sort of his his rationale.

1:09:02

* Okay.

1:09:05

* Alright, so let me share. Does that make sense?

1:09:06

* Thank you.

1:09:14

* And so then another question, when was blood in this study taken in relation to cancer diagnosis? Was it taken before the cancer diagnosis?

1:09:15

* Or after the cancer diagnosis.

1:09:23

* Okay.

1:09:31

* Anybody, anybody at all?

1:09:35

* What's that actually?

1:09:38

* It was after exactly right. So they identified the cases, they identified the controls, and then they took blood.

1:09:40

* Now this is important because for many reasons, when you're asking about with a questionnaire you might have recall bias. You might have recall bias.

1:09:46

* In this case, with the biomarker, the cancer itself can often influence bias. In this case, with the biomarker, the cancer itself can often influence levels of different biomarkers actually.

1:09:55

* Okay.

1:10:08

* So it's something to take into account with this type of case control study that you can think that the cancer, for example, might lead to immuno suppression and therefore might lead to reactivation or increased viral load etc.

1:10:09

* So you want to kind of think about with these types of study where the when the blood was taken in relation to the cancer being developed.

1:10:14

* And as you interpret things. So these are the results of the study. The first column or data looking at the association for primary hepatacella persona on the right is metastatic liver cancer.

1:10:21

* So they actually, this was kind of early on in this type of literature. They weren't exactly sure which was the right biomarker to look at.

1:10:37

* So they looked at hepatitis B surface antigen as a measure of active and chronic infection, other 2 other types of biomarkers and then compared to people who are negative for both of the hepatitis B biomarkers and what they showed was the really strong positive association between hepatitis B surface antigen and the risk of primary liver cancer.

1:10:48

* There was a suggestion of an elevated risk, but not really as substantial for the hepatitis B surface antigen.

1:11:06

* And the reason is that these other 2 biomarkers are not really specific for chronic infection.

1:11:18

* Yeah.

1:11:29

* They might be kept capturing passive infection, but not chronic infection. And then it was interesting, really no association for hepatitis B surface antigen with metastatic liver cancer, what was interesting was it did seem like the fact that these people have metastasis in their liver may have reactivated past infection and that's why you're seeing this kind of interesting positive association.

1:11:30

* So that was kind of one of the early studies. And now since many studies including cohort studies have confirmed this strong positive association.

1:11:48

* This was a really important cohort analysis of pregnant women in Taiwan. You can see the cohort was over 2 million pregnant women where all of them had a papatized v. Surface antigen status at the time of pregnancy enrollment.

1:11:56

* And what you can see here is looking at the hazard ratio for all causes of death except for liver cancer and those comparing those who are positive versus negative for hepatitis B.

1:12:16

* Really no association. Excess risk of developing death from liver cirrhosis. As well as a really strong positive association for death from palace cellular carcinoma.

1:12:31

* This was, a really interesting study as well that just looked at instead of the blood levels of the imagin for hepatitis B also looking at how viral load from the DNA might play a role.

1:12:45

* And this was a, this is different from the hospital based. Case control study because here what they did was they took a cohort study.

1:13:06

* Okay.

1:13:32

* From the Shanghai's men in women's studies. They had 56,000 women who gave a blood sample in 1,997 to 2,000 46,000 men who gave a blood sample between 2,002 and 2,006 none of them had primary liver cancer they then followed them respectively until 2,012 identified primary liver cancer cases.

1:13:33

* Okay.

1:13:38

* It's a sampling and identified controls and then went back in the freezer and pulled out the bloods.

1:13:39

* Okay.

1:13:45

* Okay.

1:13:59

* From the freezer to test the biomarker so here you don't have that reverse causation that the cancer itself is isn't likely to be causing the reactivation of the virus and what you can see here is that those who had hepatitis B surface anogen but low viral load the odds ratio for primary liver cancer was 2.2, but in the presence of both high viral load

1:14:00

* and high surface antigen, you see this strong positive association on problem, primary liver cancer.

1:14:11

* No, hepatitis C, virus is looking globally just at the prevalence.

1:14:18

* Hepatitis Ca virus around the world. A lot of geographic variability. And similar to hepatitis B, there's now been a number of studies that have really established a strong and causal association between hepatitis C infection and the risk of hepatcellular carcinoma.

1:14:19

* This, again, was just looking at a cohort of 20,000 residents in Taiwan.

1:14:46

* They were enrolled in 1,991 none of them had cancer at that time they were followed respectively through 2,008 during which time 477 of them developed incident, hepatitis, or carcinoma.

1:14:52

* That what the question they wanted to look at not only was is hepatitis C alone in important But what about hepatitis C and hepatitis B together?

1:15:07

* So in the reference group for both of those was being negative for both infections and the blue bar represents the incidence rate per 100,000 women and the green bar represents the incident rate per 100,000 men.

1:15:15

* The first is for those who are only positive for hepatitis B surface antigen. The second after that is those who are positive for hepatitis C viral infection and though those for both positive.

1:15:38

* So compared to those who were negative for both infection, the hazard ratio, 95% confidence in drills for having both infections was about 18 to nineteen-fold greater risk of primary.

1:15:53

* Does this suggest there's having both viruses is worse and having any one virus alone.

1:16:08

* And I guess vice versa is there an independent effect of hepatitis C infection on hepataselia carcinoma.

1:16:22

* Based on this data.

1:16:30

* Okay.

1:16:33

* Okay.

1:16:44

* Just for a show of hands, I'm gonna stop sharing. Here, just a raise of hands.

1:16:45

* Who thinks this demonstrates? A stronger increase in incidents. Of having both. Viruses compared to any one virus alone.

1:16:47

* Raise your hand if you're on the zoom just

1:17:00

* And who's perfect? Anybody else and who thinks it doesn't suggest a stronger effect of having both viruses and any one virus alone.

1:17:04

* Okay.

1:17:22

* Okay.

1:17:29

* Okay, some people are not voting. No problem. So yeah, I think these, data to me, if I look at this data given that you see, the increase instance rate per 100,000 people for those who have both infections compared to any one infection alone to me suggests that there's synergy in in terms of increased incidence of hepasolar cursing of having both

1:17:30

* infections.

1:17:45

* Now I'm gonna turn, change gears and talk about aflatoxin. So alpha toxin is also considered a class one carcinogen.

1:17:48

* It's a food contaminant. Remember Ed was talking about different ways in which diet can play a role in cancer.

1:17:53

* Risk? Well, aflatoxin and it's association with a padicola carcinoma, I think is a classic example of a food contaminant.

1:17:59

* So There are certain types of molds. That grow on corn, nuts, and beans, and particularly warm and humid climates you can see in this picture here on the upper right that's what the mold looks like that can produce a toxin called aflatoxin.

1:18:12

* And this is kind of a around the world. You can see in green are countries with very, very lower prevalence of this and the red or areas of the world with the higher prevalence of epitoxin as a food contaminant.

1:18:30

* So there was a really interesting study that was done in the Shanghai Men study that we just talked about among 18,000 men.

1:18:43

* They had actually both Food frequency questionnaires where they ask people, hey, did you eat corn?

1:18:52

* Did you eat beans? Did you eat nuts, etc. And then they also had urine.

1:18:57

* So when they assessed afflatoxin or measured afflictoxin based solely on the food frequency questionnaire, And then they compared high versus low dietary intake.

1:19:04

* Okay.

1:19:19

* There didn't look like much of an association between aflatoxin in the diet and risk of a patasilo cursor. Right? Can you see that?

1:19:20

* Okay.

1:19:24

* Like for those who were categorized as high aflatoxin based on the food frequency questionnaire, essentially no association with Hao Parsonoma.

1:19:25

* Versus when they use biomarkers and they use 2 different types of biomarkers in urine.

1:19:33

* One suggested, you know, if you have the presence of the DNA addict for aflatoxin, the risk of hepatito carcinoma was nine-fold greater compared to those negative for the addict.

1:19:34

* Why do you think, why do you think this is? Why do you think you think there was a difference between the food frequency questionnaire and using the biomarker.

1:19:53

* What does this suggest to you?

1:20:03

* Do you think, do you think the by which data do you believe, I guess?

1:20:10

* Raise your hand if you believe the food frequency data more so about a measure of aflatoxin.

1:20:16

* Alright, raise your hand if you believe the data that alpha toxin measured as a buyer marker.

1:20:23

* Yes.

1:20:30

* Yeah. Exactly, right. So this is a case where it's it can be hard. To measure the level of a contaminant because, you know, especially our food now is really global, right?

1:20:31

* And so it can be, you know, maybe there are certain farms where or certain batches of food where the aflatoxin was present because the mold was growing because of this season the food was growing.

1:20:42

* So it can be, here we can see questionnaires can be great for measuring diet in some capacities for alpha toxin it was not so great.

1:20:56

* So affluent toxin now is considered a group one carcinogen because of its association with a patasalic persona.

1:21:04

* In the United States and Europe. Particularly because hepatitis B. And see infections are lower.

1:21:13

* Particularly since now in many countries there's vaccination against appetite B, other causes of primary liver cancer have really started to emerge as likely risk factors primary liver cancer.

1:21:20

* They're kind of many of these are related to metabolic health. Alcohol seems to be its own risk factor independent of viruses.

1:21:36

* His concept of non-alcoholic fatty liver disease because of increased consequences on metabolic health.

1:21:47

* And then there's 2 factors where there's evidence suggesting an inverse association. Coffee consumption.

1:21:54

* Thank you.

1:21:59

* Oh.

1:22:06

* And aspirin seemed to be protective. For lowering the risk of primary liver cancer. So this figure here kind of summarizes.

1:22:07

* The population attributable fraction. For hepatitis, carcinoma.

1:22:10

* For different risk factors. And I kind of just want to highlight. This if we look at the first column is hepatitis B virus hepatitis C virus.

1:22:18

* You can really see pretty big variability. So in sub-Saharan Africa, a big proportion of hepatitis cellar carcinoma risk can be attributed to hepatitis B.

1:22:27

* And C virus because the prevalence of the virus is much greater. Whereas if you look in other parts of the world, let's say in Western Europe.

1:22:36

* It's much lower. In contrast, you can start to see things like alcohol, obesity being much bigger risk factors in Western Europe as well as in other parts of the world.

1:22:49

* So you can really see how the although the relative risk of associations of hepatitis B virus and the risk of a palace cellar carcinoma seemed to be pretty similar across different populations.

1:22:56

* So the size of the effect of the risk factor and the cancer is similar, the prevalence of the exposure varies.

1:23:16

* And that's why the proportion that's attributable to each of these factors differs in different parts of the world.

1:23:22

* And as I mentioned a little bit earlier, all of these things together have a lined in this model of how primary liver cancer, particularly a pascellular carcinoma, develops.

1:23:32

* All of these major risk factors do damage and lead to chronic inflammation of the liver, which leaves to liver disease.

1:23:44

* Cirrhosis of the liver that ultimately can lead to tumors occurring. So this model of this chronic inflammation, but things like aflatoxin and hepatitis B virus actually can do direct.

1:23:54

* Damage to the DNA. Itself, but all of these are through this model of Passover carcinoma.

1:24:11

* So in the last bit, I just want to end with a really interesting cancer. Clandio carcinoma which is much more rare.

1:24:18

* Yeah.

1:24:53

* Primary liver cancer so in most population the majority of primary liver cancer is due to hapadascellular carcinoma, but in certain selected Asian populations it seems like colonial carcinoma is a larger proportion so parts of Thailand's in in Hong Kong in parts of China and in particular there's a part of Thailand that where the majority of primary liver cancer is due

1:24:54

* to clandio carcinoma. Really interesting descriptive epidemiology that led researchers to wonder why was Clantio carcinoma occurring as such a predominant component of primary liver cancer.

1:24:57

* See.

1:25:16

* Well, in particular in this this part of Thailand so, this is looking at Thailand in the countries.

1:25:17

* That are the highest, incidents, of clandio carcinoma also seem to have a very high prevalence.

1:25:19

* Of a an infection known as liver flukes. And this is a type of parasite, a form of a worm.

1:25:29

* That preferentially infects the bile ducts. And if you remember The bile ducts are where colonial carcinoma comes from.

1:25:39

* So hepatitis, L to have had a cellular carcinoma, glandio carcinoma comes from the bile ducts and it was discovered that by consuming raw foods whether it was fish and snails and this this picture here D is what these liver flukes look like.

1:25:47

* These can actually then infect the bile ducts and lead to the development of clandio carcinoma.

1:25:59

* It's largely preventable. By cooking fish, it kills the liver flukes and therefore will not lead to cancer forming.

1:26:13

* So, Claire, liver flicks are considered now a group one carcinogen. Again, really interesting.

1:26:23

* Example of how descriptive epidemiology of this cancer led to the discovery of liver flukes.

1:26:31

* And these are 2 different types of liver flukes that are considered to be group one carcinogens.

1:26:38

* So presence of these liver flukes is associated with about a 5 to tenfold greater risk of clandio carcinoma compared to those who do not have the liver flukes.

1:26:41

* Just in terms of other risk factors for clandio carcino, it does seem that hepatitis B and C.

1:26:50

* Viral infections are associated alcohol seems to be a risk factor as does obesity diabetes, maybe not smoking, but these are thought to be probable risk factors for clen do carcinoma.

1:26:59

* So just to end this conversation and summary, infections are a major cause of cancer, but they're also largely preventable.

1:27:11

* So we can think about with hepatitis C virus, for example, now there's actually treatment.

1:27:19

* Yeah.

1:27:30

* For hepatitis C. And the question is, by the time someone's discovered to have hepatitis C it often can be after a lot of damage has been done.

1:27:31

* Okay.

1:27:36

* So big question is can treatment of hepatitis C. At that advanced stage lead to prevention and that's an interesting question right now.

1:27:37

* We've talked about vaccinations for against hepatitis B viral infection. We've talked about screening.

1:27:45

* For preventing from the cancer occurring in the first place and also things like treatment of a H by lorry as well as general cleanliness and hygiene principles.

1:27:48

* And as I as we talked about, infections can be promoters. Leading to inflammation.

1:28:05

* They can be initiators of cancer. Hepatitis B virus is really interesting as a model of both an initiator and a promoter.

1:28:12

* Liver cirrhosis really seems to be this unifying model understanding the ways in which ideologic factors are leading to cancer.

1:28:20

* Warming. And it includes both viral and non-viral causes and as the prevalence of some of the viral causes is going down.

1:28:28

* Okay.

1:28:45

* The non-viral causes may seem more strongly associated also as things like poor metabolic health are coming into different populations, obesity is growing, those non-viral causes may emerge as more a greater proportion of the population.

1:28:46

* Okay.

1:29:03

* And I think hopefully also this talk gave some examples of how we use biomarker-based studies in cancer epidemiology and some of the principles of those biomimicry based studies as well.

1:29:04

* So I'm going to stop sharing in the last minute any any questions.

1:29:06

* Any observations, any thoughts?

1:29:14

* Okay.

1:29:17

* Okay, great. Well, wonderful to see you all. Colleen and Michelle, any final thoughts or words or comments about the class?

1:29:22

* Just make sure we're working on your projects and if you're hoping to meet with us the designated person, and if you're hoping to meet with us the designated person for your specific cancer.

1:29:30

* Yeah, and I might even add to that just, to do a direct email rather than going through Canvas for some reason Canvas sends my emails into a weird Mailbox that I don't check off in so just email us directly to set up a time to meet that we really just want to talk about the presentation in your risk factor and give any advice we can.

1:29:44

* YeahAll rightThank you

7

* Majority of patients who get pancreatic cancer, actually close to 90% actually die from the disease.

7:30

* And that really has a host of different reasons. Usually at this point in the class we go around and we sort of ask people to think about what are the.

7:36

* Reasons they would think a cancer would have high mortality. You know, why would one particular cancer lead to more cancer deaths than than others.

7:45

* And usually what happens when we do that is people name a whole host of different things, which I'll show you on the next slide.

7:54

* That could be for any cancer type right that are not necessarily specific to pancreatic cancer. And they're just general things that could lead to high mortality from a cancer.

8:01

* But pancreatic cancer checks all of the boxes, meaning all of the things that people mentioned and it really does have essentially the highest mortality of any major cancer type.

8:07

* So as you might think, there's a number of things on this list. So there's a limited number of predisposition factors that we know of and they're mostly lower penitence risk factors.

8:21

* The early warning symptoms and signs are relatively nonspecific. Something we've been thinking more about lately is how we use these things in aggregate to try to find patients in the general population who are developing this disease.

8:32

* We don't really screen for pancreatic cancer. Although I'll show you a couple of examples now where we're starting to, and I think that's starting to raise some hope that if we can identify people at higher risk.

8:47

* That we actually can find it early with screening tests that we may improve, survival. And again, I'll give you a couple of examples where that's starting to be done.

9:01

* Pancreatic cancer spreads very early. So most cancer types, many of the other GI cancers that I take care of like colon cancer, it's a pretty stereotyped small tumor, bigger tumor, lymph nodes get involved, becomes metastatic.

9:06

* And Pankretic cancer doesn't really follow that paradigm like many other cancers. You can have quite small tumors in the pancreas and already end up with distant metastases and it will sometimes just skip the nodes altogether and develop the task to seize.

9:27

* So the problem is it spreads quite early. And it's development. Except biologic reasons for that at the molecular level are not that well understood yet, but it's very invasive and it tends to invade into both lymphatics and the Venus system very early on.

9:40

* I mean, this may be part of the reason why it's spread so early. And then people get really sick.

9:51

* With this disease. This is a cancer where people lose a lot of weight. They can't eat or drink well.

10:01

* They get a lot of fatigue. They get nausea vomiting other issues. And actually that sometimes really causes us problems and it prevents us from being able to treat the disease as a aggressively as we would like.

10:07

* And as I'll show you, patients with pancreatic cancer, about half the patients in the United States.

10:19

* If they develop metastases from their pancreatic cancer, get only one line of therapy and then they pass away.

10:25

* Right, and that's again in sort of modern age of. Oncology care that's quite uncommon right you can in women with metastatic breast cancer use 10 different therapies over in multiple different years.

10:32

* And pancreatic cancer, we just don't have that. Our momentarium in the same way.

10:44

* And that sort of goes to the next point, which is this tends to be pretty refractory to the treatments we have.

10:49

* They're not a lot of chemotherapies that work. And immunotherapy, which we think of a lot now for other cancers don't work in pancreatic cancer, at least the immunotherapies we have today.

10:54

* A lot of work going on to try to change this. And then the last is, you know, some of the tumors we've seen improvements in treatment and lower mortality has either been because of immunotherapy or because of new targeted drugs that have been able to say in like EGF army and lung cancer, keep people alive for many years or help cure the cancer after tumor reception.

11:04

* And that's been difficult in pancreatic cancer so far. I'm not going to talk a lot about it, but there's a sea change coming, which is that there are a whole host of drugs out there now that inhibit an oncogene called KRAS that are either in the in the preclinical space for now just hitting phase one trials.

11:27

* That are gonna hopefully change some of this in pancreatic cancer. Alright, so to start with one of the main issues we talked about is that this disease presents late, right?

11:46

* So it tends to present it in advanced stage. It spreads very early. So if you look at this, you can sort of see that on the bottom is your AJCC stage.

11:57

* So stage one and 2 mean it's localized to the pancreas. No evidence of metastases.

12:07

* And it doesn't invade blood vessels around the tumor that prevent reception. This is really the stage or stages one and 2 that we can cure in some instances.

12:13

* In fact, if you find a stage one tumor, which is a small tumor with no node involvement, you actually can cure over half of these people with surgery and aggressive chemotherapy.

12:22

* But the problem is this is a very small, in this case, 5% or less of patients. Most patients either present with larger tumors that haven't spread.

12:33

* Larger tumors that invade vessels, blood vessels, which is locally advanced disease or metastatic disease.

12:43

* And you can see on the Y axis is the 5 year survival rates, they get very low very fast, right?

12:48

* As the stage gets higher. And so really once you end up even with a localized tumor that gets bigger or has lymph node involvement or a tumor that invades blood vessels, you really don't care a lot of those patients.

12:54

* So really if you want to to cure more people we're gonna have to move leftward more towards the green right in this diagram than we are in the blue in the yellow currently where over half of patients even present with distant metastases.

13:02

* I'm at the time of their diagnosis. So really a sea change is needed in addition to new therapies moving things to earlier diagnosis.

13:21

* So I thought I would start off with. A couple of groups for which we do actually do some sort of surveillance or screening.

13:30

* For pancreatic cancer there's really 2 groups like this One of those that have a very strong family history and or known genetic inherited mutation and another are patients that have cystic lesions of the pancreas.

13:38

* If you add this up, it's about a quarter of patients with pancreatic cancer. The problem is who ultimately get pancreatic cancer.

13:52

* The problem is many of these patients are not known and I'll show you there are a number of genetic mutations related to this, but there's quite a number of families that don't know they have these mutations and you only know you have a cystic lesion if you've had some sort of scan that showed it often for other reasons because the sister often asymptomatic.

13:57

* So although there's about a quarter where we could potentially do surveillance, most of these are not actually found by surveillance.

14:17

* But let me give you a little sort of discussion of the, on genetic risk, cause this is where some of the data has started to emerge really just in the past 2 or 3 years.

14:24

* Suggesting that screening may be useful if you can find a high enough risk group that it is, appropriate.

14:34

* So this is a study now it's a few years old, published in, Journal of the American Medical Association, from a Mayo clinic study where they basically took 3,000 patients with pancreatic cancer and they did panel sequencing of the germ line and what they were trying to do is identify what were germline mutations that were in patients with pancreatic

14:41

* cancer. The ones on the top, these first 6 were ones that were statistically significantly different than when they compared to sort of a population database called Nomad.

15:03

* And what they saw is a few of these mutations were in jeans that we know about, right?

15:14

* For other cancers, really all of them, right? So BRCA one, BRCA 2, ATM, and others that predispose to other cancer types, right, to breast cancer, ovarian cancer, and others.

15:15

* And this really wasn't the first study that had done this, a number of studies, including a couple of studies we published from Dana Farber, but this was the biggest.

15:30

* I mean, it really, again, emphasize that there are a number of inherited mutations. That are related to development of pancreatic cancer.

15:37

* This is then led to a host of recommendations about the potential for screening. This is a review article that we wrote.

15:47

* Leah Billers, a junior faculty member at Dana Farber. That talked about these different syndromes, right, based on the genes that are known to be inherited that have pathogenic mutations and relate to pancreatic cancer.

15:56

* And there's now screening recommendations by age and how to do this screening. So let me just tell you what the screening is and then I just wanted to show you some of the data from the largest.

16:04

* Sort of follow-up we have of these patients to try to suggest and and sort of make the case that screening may be useful if you can find the right people to do it in.

16:18

* So what was done for these individuals, people with familial risk of pancreatic cancer, either because of inherited mutations or also multiple first degree family members within the same family was a combination of 2 types of imaging tests.

16:33

* One was an endoscopic ultrasound. You place a probe through an endoscopic down someone's throat into the stomach and then around through the small intestine, the duodenum, which is here.

16:48

* And the probe then looks at the pancreas and it's trying to find small lesions in the pancreas.

16:59

* That's sort of what this is denoting what this is denoting. And you can find small cancers this way, before they have spread.

17:05

* But it is invasive, right? It's an endoscope that requires an invasive procedure.

17:14

* Procedure requires some sedation. So we also have been using MRI, which obviously does not require sedation.

17:18

* This is a procedure where you use, magnetic resonance imaging together with what's called an MRCP just to pick up the ductile structures.

17:26

* Again, where you can now start to delineate the anatomy and try to find where the pancreatic duct is sitting where the pancreas is sitting and then identify small tumors.

17:34

* So we've been doing this for a little while, but the efficacy of it was not really that well understood.

17:44

* And so this is a relatively recent article. That has started to show along with a couple others actually that there may be benefit to doing surveillance among individuals who have high risk.

17:50

* Because of genetic mutations or familiar risk. This is called the CAPS protocol. And it's based at Johns Hopkins, includes a number of different academic centers, in this case 8 of which Dana Farber has been one for many years.

18:02

* I mean this was a study that looked at around 1,700 individuals. And look to see if someone stayed in this screening program, which is primarily once a year doing either the endoscopic culture sound that we talked about or the MRI.

18:10

* Could you find early cancers? This is not a randomized study. It's really a sort of surveillance follow-up study where each of the institutions followed a similar surveillance program.

18:30

* And I think what you can see here in the box is that yes, there were cancers that were found.

18:42

* There were 26 actually pancreatic cancers. And stage one and 2, like we talked about are really the stages where cure can be possible, mine where we have the ability to do surgery, chemotherapy, and try to remove the tumor.

18:47

* And 3 quarters of the patients who were, sort of faithful to the screening program doing this every other year approach.

19:01

* We're found with early stage cancer. And you can contrast that to what we talked about before where that really sits more at 15 to 20% in the population.

19:09

* And then there were a set of individuals who sort of fell out of surveillance for whatever reason.

19:19

* They stopped coming. It's actually not as you might suspect the easiest thing. To stay in surveillance when you have to do these types of procedures once a year.

19:26

* It's easy over time for people to sort of say, I'm gonna stop doing this.

19:30

* But if that happened, the rate of finding early stage disease, stage one and 2 for the people who fell out of the surveillance program were just what you would have expected in the general population, which is again in that 15 to 20% rate.

19:38

* And then if you looked at survival, there's 3 curves here on the Kaplan Meyer curve for survival.

19:52

* The top curve is actually where several patients that were found. To have a pre invasive lesions in the pancreas, sort of like DCIS of the breast or a polyp in the colon and those patients had those removed and those were almost universally cured, right?

19:58

* This is overall survival. They did not develop disease. They died from something else the individual passed away. So you could find 3 million, and those people could be cured.

20:15

* And then you could also with the blue line in the screen detected patients. Those are individuals who had a blue line in the screen detected patients.

20:25

* Those are individuals who had a blue line in the screen detected patients. Those are individuals who had early stage disease.

20:33

* The cure rate was much, much higher and patients did much much better than those here in the red line.

20:34

* Who, who had their cancers diagnosed outside of surveillance? So the 5 year survival rate among those who had prema ligna lesions was a hundred percent.

20:40

* For those who had the screen detected cancers, which are mostly stage one and 2. Is almost 3 quarters and unfortunately like we usually see in regular practice no patients were alive at 5 years if they had their cancer diagnosed outside of screening.

20:50

* So there's now, they're now probably 2 or 3 studies like this that start to suggest.

21:05

* If you can look in a high risk population and use some imaging tests that we have available even now, we can push.

21:10

* The staging to earlier stage disease and potentially find disease early. Okay, the problem though as we mentioned is there's very few patients we know of in the general population who have a risk like this and we'll come back to that idea.

21:18

* Because of this and a couple other studies, germline testing is now recommended. So looking for inherited mutations in every patient who's diagnosed with pancreatic cancer.

21:32

* That obviously doesn't help that patient. Right have the disease found early they've already you know developed the cancer but what we now do is what's called cascade testing, whereas all of the first degree family members, if the pro band, the person with cancer is found to have a mutation.

21:43

* All of those family members are then offered germline testing. And if they have the mutation, they then end the type of screening program that we just described.

21:56

* With the hope that this will then allow us to start to find more and more individuals who should undergo screening.

22:09

* The other, and I'm not gonna spend much time on this, but the other. Place, the other population where we will do some screening or surveillance is among those that have cystic lesions of the pancreas.

22:16

* Again, these are mostly asymptomatic and they're not things that we would know about unless people had scans for another reason for the most part.

22:25

* There's a lot this paper if you're more in if you're interested there are a number of different guidelines around how to manage system lesions in the pancreas just quite complicated.

22:36

* This is a European set of guidelines. Really to highlight there are a number of different kinds of SIS.

22:46

* They're not all the same. But the one that you most often hear about is an IPMN, which is an introductory papillary mucinous neoplasm.

22:51

* The most important thing about IPMS is they themselves are not invasive, right? They're not an invasive tumor that will spread to other areas of the body.

23:00

* However, they have the ability to transform to become an invasive cancer. And that's really the important piece is how do we manage these either by follow-up or ultimately by surgical removal to prevent cancer from ever developing, meaning invasive cancer.

23:08

* And so you can see among, again, a number of different guidelines that exist. You either end up in, you don't need follow up or you should get MRIs and US is just like actually what we talked about with the familial risk.

23:24

* Or you should go to surgery. And again, this is an opportunity. And a window for us to try to find people who should have a pre-molignant lesion removed.

23:38

* Again, very much like what a colonoscopy does in colon cancer. These lesions are related to about 10% again as we talked about at the beginning of pancreatic cancers and many people don't.

23:48

* No, they have them, but again, it is another place where we can start to find this disease earlier and try to treat it more effectively.

24:00

* Alright, so if we then think, well, what happens in the other 75%, right? Why do these people get pancreatic cancer and what can we do to try to find the cancer earlier, which really is what we need to do in order to cure more patients.

24:08

* So there are a host of different features and Laura, I mentioned a couple of these in the sort of lead into this.

24:23

* That are related to pancreatic cancer risk and we'll sort of review them. I tend to put them in sort of larger categories that help us think through some of the biology of the risk factors.

24:30

* But among the initial set are demographics, right? So there are groups of individuals that we know are at higher risk of pancreatic cancer in the population.

24:41

* I think to start with the most strong risk factor for pancreatic cancer is age, right? This is tends to be an age of older adults, although that is changing as people have likely heard, GI cancers in particular seem to be rising in younger individuals.

24:50

* Colin cancer gets a lot of or colorectal cancer gets a lot of attention. For that, but pancreatic cancer is actually doing the same.

25:06

* But generally speaking still, it is a cancer that tends to be an older individuals. The median diagnosis is around the age of 70.

25:14

* It tends to be a higher rate in men in Ashkenazi Jewish individuals, which may have something to do in part with the familiar inheritance of BRCA mutations.

25:22

* As we talked about, those are known risk factors for pancreatic cancer and they do tend to be enriched in the Ashkenazi Jewish population.

25:35

* And it tends if you look worldwide it tends to be more in Western culture cultures than Easter.

25:43

* In the US, if you look at populations within the United States, African-americans have the highest risk.

25:48

* And so you can see from the 2 figures here you can see again as the rate per 100,000 individuals by age.

25:51

* You can see that there's a substantial increase as you hit 45 to 50 and then a very steep increase that seems to mostly continue.

26:02

* As people age. Slightly higher in men than in women. That's the green versus the blue.

26:06

* Right, and then if you look at men and women by race ethnicity, again, black Americans tend to have higher risk.

26:18

* In both men and women compared to their counterparts of other races.

26:25

* So if we think beyond some of the demographics, what are some of the other risk factors that that predispose individuals to get this disease.

26:31

* Laura, I mentioned at the beginning that what I would sort of put into this category of altered metabolism.

26:41

* There are a number of features related to systemic metabolism, how we process nutrients, weight, exercise that are risk factors for pancreatic cancer, particularly obesity, physical inactivity is a little less consistent, but seems probably to be related.

26:46

* And then also diabetes. And if we start to think a little bit, well, what are the relative risks? Right?

26:57

* We talked to the beginning, part of the issue for some of the risk factors we do know. Is that the penitence, meaning the likelihood that they get the cancer, when they have this risk factor tends to be pretty low.

27:07

* So there's not really like a smoking and lung cancer relationship here. These are much more attenuated relative risks than you would see in a circumstance like that.

27:21

* So if you look at obesity and this is sort of long term obesity, what you can see is the relative risk is about one and a half to 2 fold.

27:30

* If you're in the obese range versus the healthy weight range. And if you have diabetes, again, this is now long term.

27:38

* So at least 5 years or longer, what you see is the relative risk is between 2 and 2 and a half.

27:42

* One of the paradoxes of this, which Laurel I mentioned in her question is that patients with pancreatic cancer tend to lose weight as they approach the time of their diagnosis.

27:52

* Which we'll talk a little bit more about. So people, if you do a case control study and you look at the time of diagnosis, patients with pancreatic cancer will often be underweight in comparison to their counterparts without pancreatic cancer.

28:02

* And again, that's usually happening as you approach the time of diagnosis. Interestingly, diabetes does the same thing.

28:16

* And this is really a quite a unique feature of this kind of cancer. You don't see this really in any other cancer type.

28:20

* So that paper from. And the MD Anderson and Mayo Clinic group, I'm led by Cress Charity.

28:30

* And what he studied over a number of years and we've done some work in this area too is that yes diabetes over, you know, a decade or longer is clearly a risk factor for pancreatic cancer again with the relatives we talked about.

28:37

* But the other thing that occurs is the cancer itself, just like it causes. Weight loss also actually causes hypoglycemia.

28:50

* The exact mechanism of this is not totally clear. We have a number of studies going on trying to figure out why this is.

28:59

* Happening at the molecular level. But this, figure is showing, which is a, from a paper from, You can see on the y-axis is their mean fasting blood glucose.

29:06

* And on the x-axis is actually the time before the patient is diagnosed with pancreatic cancer here, time 0 is over here to the right.

29:19

* That's the blue, right, of the people who have who develop pancreatic cancer. And then the red are the people who don't develop pancreatic cancer.

29:28

* This is a matched. Case control design. And what you can see is that people with pancreatic cancer, particularly in the 2 to 3 years before they're diagnosed, start to develop hypoglycemia and the blood sugar rises.

29:34

* And this is not something you tend to see in patients without pancreatic cancer. And in fact, if you look at a population level in the United States, it's about half a percent of people who develop diabetes.

29:45

* After they turn 50 so older than the age of 50 who actually have pancreatic cancer as the cause of their diabetes.

30:04

* Right? And so lots of diabetes is for all the reasons we know, right, not related to cancer at all.

30:07

* But about one in 200 to one and 2 50. It's actually from an underlying pancreatic cancer that's just not been diagnosed yet.

30:13

* Because of this, there's some large studies going on now. And that's a combined effort between the endCI and NIDDK to try to study patients with new onset diabetes.

30:25

* Of older age to try to see whether we can use that as a potential population for screening. I mean, there's a number of studies going on and we've been involved in some of those too.

30:36

* But again, a very unique feature of pancreatic cancer that it actually causes diabetes in addition to diabetes being a risk factor.

30:47

* Yeah, please.

30:57

* Brian, can I see a quick question? This is Laura. I'm just on the figure that you showed.

30:58

* Is, is there any suggestion that at the time of the initial onset of hypoglycemia that the tumor was actually there but just not diagnosed yet or is it really that the the cancer is developing and growing within that 36?

31:00

* 30 to 36 months.

31:17

* Yeah, so it's a great question. So. One of the troubles we have with this disease is that We there are times that the cancer is there, but very hard to see.

31:19

* The pancreas is among the most difficult organs to image in the body. So scans have a hard time sometimes picking it up.

31:30

* We have Well, I would say Sresh Charlie did a really interesting study where they went back and tried to find scans from the time that people became hyperglycemic.

31:32

* And in some instances, they actually could see a small mass that was missed when the patient had the scan.

31:49

* But that they obviously had this scan for some reason, right? It wasn't for pancreatic cancer at that time because they didn't know they had pancreatic cancer.

31:55

* So it was a scan that was done incidentally. But yeah, sometimes you can. What we see though is that As the tumor is growing and the as it gets bigger, you're more likely to become hypoglycemic.

32:03

* So it does seem to be correlated with the size of the tumor. Which then obviously it has implications for diagnosis.

32:16

* What I would say though is as you start to get within a year or 2 before diagnosis, You can sometimes start to see evidence of a mass there.

32:25

* If you go back and look, that might have been missed. And then there's some been a couple of really interesting studies recently.

32:33

* Using machine learning and radiomics to try to look whether you can see. On CT scans.

32:36

* 18 months before someone was diagnosed, Are there differences in the pancreas that may not have conglomerated yet to make a visualized mass?

32:44

* And the answer to that is yes, there's actually been a couple of very high profile papers, including one recently in Nature Medicine that did this.

32:54

* And so I think that when they're getting hyperglycemic, the cancer is there.

33:03

* I'm not sure always will be able to see it, but if you did serial scans, I think you would because it will eventually show up.

33:08

* Is that answer, that what you were thinking about?

33:16

* Yeah, absolutely. That's fantastic. Thanks.

33:19

* Okay, yeah, I think it's very a very cool area. I'll show you a study that we did recently where we also were using CT scans.

33:21

* We collected from before diagnosis. There are clearly signatures of the cancer that you can see before they're diagnosed where there's a window I think that early detection could be possible.

33:24

* Alright. So another feature that we usually think about related to risk factors for pancreatic cancer are things that lead to inflammation and they can be sort of inflammation in the pancreas, they can be systemically, but really inflammation in the pancreas in particular.

33:42

* And it's interesting in a number of different mouse models of pancreatic cancer. This type of inflammatory insult is almost required in order to see the tumor develop.

33:59

* So there's clearly an interplay between inflammatory issues in the pancreas. And the development of the cancer.

34:08

* There's a few on this list here as we're sort of going through and talking about risk factors that are we think related to inflammation.

34:15

* One is cigarette smoking, 2 is heavy alcohol use, and then 3 is chronic pancreatitis, which is by definition a in chronic inflammatory condition of the pancreas.

34:23

* And again, these all have relative risk modest, but relative risk for pancreatic cancer, that are in sort of the one and a half to three-ish kind of range.

34:35

* For smoking, this is the range you tend to see for current smokers versus never smokers 2 to 2 and a half.

34:45

* Again, you smoke more, you smoke longer, the relative risk tends to be higher. I mean, it's been actually really interesting.

34:51

* We're in the middle of doing a study around this now. You don't when you sequence pancreatic cancers at the DNA level.

34:58

* You don't see mutational signatures of cigarette smoke, right? So they've been many studies that have shown in cancers like lung cancer or had a neck cancer, we have direct exposure of epithelium to the toxin, in this case the toxins in smoking, you get stereotype DNA mutations that develop that you can pick up when you sequence the tumor.

35:05

* In pancreatic cancer, we don't see that. So meaning that it does not seem to be a direct toxic effect of the carcinogens in the smoke on the DNA in the tumor.

35:27

* And so what we've been studying now is there's been this thought that this is an inflammatory insult, but there's not a lot of data yet to show that there's some data in mouse models as I was mentioning, but not so much in humans.

35:37

* And so we've been trying to figure out can we start to look at this by looking at pancreatic cancers in the lab both at the DNA level to figure out well what mutational spectra do they have and then also by looking at among smokers compared to non-smokers, what's the micro environment the tumors are living in?

35:48

* Is there more evidence of inflammatory insults around the tumors? So I think this is an interesting area where the reason smoking is related to pancreatic cancer is different than you might think for some other cancer types.

36:06

* And then alcohol and chronic pancreatitis, they these may work similarly. I think as folks likely know, people who drink a lot of alcohol do get pancreatitis.

36:19

* And so there may be something here that's linking those 2. And then chronic pancreatitis, which can happen from a number of different reasons.

36:28

* It can be stones in the pancreatic duct, it can be medications. Again, it can be heavy alcohol use.

36:35

* There's inherited forms of pancreatitis. These all are related to an increased risk of pancreatic cancer.

36:41

* I would say chronic pancreatitis also has this same interesting relationship that diabetes does.

36:49

* And obesity versus weight loss does. Which is that a tumor in the pancreas sometimes causes pancreatitis.

36:55

* So as you can sort of get a sense of reverse causation in studies of pancreatic cancers really important to think about.

37:02

* So if you look at people who've had a cue pancreatitis, they actually have a substantially higher risk of pancreatic cancer much more than 2 to 3.

37:05

* In the next 12 months. But that's because the cancer caused the pancreatitis. So what sometimes happens is pancreatitis can happen from blocking of the ducks that drain enzymes out of the pancreas into your small intestine, which is one of the main jobs that the pancreas does.

37:16

* The tumor will sometimes impede the flow of the enzymatic fluid out of the pancreas and when that happens they get pancreatitis.

37:34

* So I will sometimes see patients in clinic who 3 months ago presented to the hospital they had acute pancreatitis, their everything was inflamed, they didn't know what was going on, and then they end up doing a repeat scan to check on things and now they see the mass and they actually had a pancreatic cancer that caused the pancreatitis.

37:40

* So again, reverse causation in this disease related to a number of these risk factors is really important. And biologically, I think quite interesting too as we think how to leverage these things for early detection.

38:00

* Right, I see. Yeah.

38:12

* And I'm sorry, Brian, there's a question in the chat. How do you differentiate?

38:13

* This in terms of causal inference. Maybe you address that kind of already, but.

38:17

* Yeah, so I agree. It is important. I think at the end of the day some of this has been defined using model systems in the lab, right?

38:20

* And and then some of them have been you defined using human data. I would say one thing to go back to the diabetes one interesting piece and then I'll keep going is one of the ways we've been able to tell from human data that pancreatic cancers cause diabetes has been that when you remove the tumor, so patients that have a localized tumor They got diabetes

38:30

* in the year or 2 before their diagnosis. The diabetes actually goes away. Which is pretty cool, right?

38:54

* That's really strange. You wouldn't have thought that, right? You would have thought if it was all risk factor.

38:59

* That as the pancreas malfunctions, right, because the pancreas makes insulin.

39:07

* If you removed the tumor in a bunch of someone's pancreas, they should become more diabetic, not less, because you're actually removing beta cells.

39:12

* And their ability to decreed insulin should go down. But in this case, you're removing the tumor and they're diabetes is getting better, which is really telling you that there's almost like a parity of plastic syndrome.

39:16

* The tumor is actually causing dysfunction. Some of it's in the pancreas, some of it is actually peripherally that's causing the diabetes.

39:32

* And so by putting sort of different lines of evidence together, we've been able to determine that there is this sort of bimodal distribution where there's a risk that comes when you have diabetes for a long period and then a risk that comes right up against the time of diagnosis.

39:38

* And we've also done some studies where we've measured markers of insulin resistance and among individuals before diagnosis where we have blood samples and again we can see this you shaped.

39:51

* Curve, which again has supported the fact that it is again has this differing biology.

40:06

* Alright, so.

40:13

* And then I'd say the last big bucket here, right? So we talked about the demographics of the disease.

40:17

* We talked about some of the exposures that are risk factors for pancreatic cancer, right?

40:22

* Things that are inflammatory related like cigarette smoking, alcohol, things that seem to be metabolically related like physical activity, obesity.

40:27

* Some of these also fall, if you think about sort of comorbid conditions, again, diabetes, pancreatitis, cystic lesions we talked about at the beginning.

40:35

* So the other big bucket then really is is inheritance, right? So either strong family history.

40:41

* Or inherited mutations. And we talked a bit about some of the rare inherited mutations. Just to review this again from this study from Mayo Clinic and mostly the thing I wanted to point out is what are the actual relative risks, right?

40:51

* We talked about what the relative risks are for smoking and obesity. What are they for genetic mutations?

41:05

* And so you can see among these most of them are between 5 and 12 fold risk, right? CDN, CDK and 2 A is.

41:11

* One of the genes that has the highest risk for pancreatic cancer, that actually is a gene that leads to familial melanoma syndrome.

41:19

* So these patients get both melanoma and pancreatic cancer. I've had a number of patients in my clinic where I talk to them and they say, oh yeah, my dad in Melanoma, I had melanoma.

41:26

* And then when we do the genetic testing, they have one of these genetic mutations that predispose them also to the pancreatic cancer, which is why I'm seeing them.

41:36

* And then you can see a number of the mutations we think about, PRCA 2 is about a six-fold, ATM about a six-fold, P.

41:44

* 53 is the cause of leaf, And MLH one is the cause of Lynch syndrome, one of the genes that cause lynch syndrome.

41:52

* That have higher risks. And you can see BRC ones actually a little bit lower. The studies I showed you where screening was effective, we think, although again, not randomized, but where we think we're able to catch some of these cancers early.

41:59

* Actually these individuals had even a higher risk than was listed here. This is purely based only on mutation.

42:13

* Those studies actually required you have at least one family member with pancreatic cancer also. And so those patients we think had at least a tenfold risk of pancreatic cancer.

42:20

* This is now a big source of debate. I'm in the field is should you require individuals to have a family history or should everyone with a BRC one or 2 mutation get screening.

42:31

* That really expands the population, right, because there's quite a number of people we now know of, PRC one and 2 mutations.

42:42

* Most of them do not have a family history of pancreatic cancer. And so whether they should also be undergoing pancreatic cancer screening is not that well-defined.

42:47

* And this is something that's now being studied to try to figure this out. Again, it may allow us to find more cancers early if we expand.

42:57

* The screening population, but certainly there's also then more complexities, right? We could cause more problems by doing them cause issues with the endoscopy where someone has a reaction to.

43:05

* To the sedation or we find some random finding an MRI that leads to, you know, having to do all this workup that turns out not to be cancer.

43:16

* So there are certainly drawbacks to expanding the screening population. And we're trying to look at how we would do that in a safe way.

43:21

* Alright. People often ask, do we know about common variance? And these are often identified in genome mind association studies or G.

43:34

* That people have. Pancratic cancer is again substantially less common than some of the other cancer types that cause a lot of mortality less common than some of the other cancer types that cause a lot of mortality.

43:43

* So it's been much harder to do these studies. Also these patients tend to not live long, right?

43:54

* So if you need to have banks specimens, banked blood samples, buffy coat, normal DNA has to come from somewhere to do these studies.

43:58

* It's not as easy to get those samples for patients with pancreatic cancer than say prostate cancer or breast cancer where there are now, you know, hundreds of these variants that have been identified.

44:07

* In pancreatic cancer, we have a couple dozen that have been identified through a series of genome might association studies that have been done over the years.

44:17

* These are actually worldwide studies. You really need studies from all over the world to do this. I'm in order to aggregate enough cases and controls and you can see that these studies that have led to the variance over here again have had a little over 10,000 cases and close to 20,000 controls.

44:25

* There's a study that's going on right now called PAN Scamp 4, which will more than double these numbers.

44:38

* I mean, those, samples are mostly sequenced. And you can see again, I think as an important point and as folks probably know from looking at these studies.

44:50

* The relative risk for each minor allele or each risk allele is very low right so it may be 1.2 or 1.1 9.

45:00

* So any individual variant that you find is not going to allow us to screen, right, a particular group of individuals.

45:06

* However, what's now started to move forward in other diseases, maybe someday in pancreatic cancer.

45:13

* Is if you aggregate these, you can generate risk scores that do allow you to segregate relative risks such that the extremes have much higher risk of the score overall.

45:21

* I might say there also are some interesting genes on this list that have the variance nearby, right? These studies are not looking for a particular gene, right?

45:33

* They're looking for a polymorphism, but there are some genes near these polymorphisms that biologically have been studied and do relate in in mouse models and preclinical work to the development of pancreatic cancer which has been sort of an interesting in road to try to understand why some of these cancers may be developing.

45:38

* The one at the top actually has some of the best data and R 5 A 2 is actually a transcription factor that helps delineate self fate in the pancreas and there have been a number of really quite interesting studies that the gene dosage effect of NR 5 A 2 actually changes the self fate within the pancreas, particularly after an inflammatory insult.

46:01

* And so again, some of these may be interesting biology to study, but still have quite a bit of work to do before this would be useful in a clinical setting.

46:21

* Alright, so maybe to sum up some sort of thoughts from the risk factor aspect and then can maybe see if folks have other questions or thoughts.

46:30

* But what I would say a number of the factors we talked about and and Ed's done quite a bit of work along these lines really relate to overall sort of health and healthy lifestyles, whether it be obesity or smoking or alcohol use.

46:32

* Diabetes and there have been a number of studies that have suggested that if you an aggregate can have a population that has a healthier set of behaviors along these lines.

46:46

* That it does look like we would prevent some pancreatic cancer from developing, right? And it may not actually be a small percentage.

47:03

* There could be a substantial percentage. So this is important, right? It's hard to get people to change their lifestyle because of pancreatic cancer.

47:07

* It's a rare disease. But certainly as other public health interventions lead to healthier lifestyles, you would hope that we may also have an effect on pancreatic cancer.

47:15

* A second is that there are now a couple defined populations for which surveillance is considered appropriate and and actually now I would say considered a standard thing we should be doing.

47:26

* Although most places in the country still don't do this. So it usually means going into a major academic center.

47:36

* If you have a strong family history, or genetic risk to then do the screening. And these MRIs are complicated to read.

47:46

* You need somebody for who does the endoscopic ultrasound who really knows how to do this in the familiar risk population.

47:54

* There's some complexities in that population in particular. But if we can identify these individuals in the population, it does seem like we can stage shift.

48:00

* And again, back to that cup study where 3 quarters of patients when they underwent this screening at stage one or 2 disease, which we generally speaking only see in 15 to 20% of patients otherwise.

48:10

* So this really, I think, has led to some, some conviction that doing this type of screening can be useful.

48:23

* There's a lot of work going on now in pancreatic exists, which is I think really interesting.

48:30

* We don't do this work in my own group, but I think it's quite cool. And it really is trying to get it this issue that as we get more and more CTs and MRIs and things as a population, we will find more and more of these CIS.

48:34

* The vast, vast majority will never become cancer. But we know a subset will. So how do you figure out what that subset is?

48:48

* So you get rid of the SIS early. I mean, there's been some really interesting studies using cell free DNA from the cyst fluid.

48:51

* So aspirating the cyst. And looking for mutations that would signify invasive disease. And then using other markers within this is fluid and then a host of clinical factors too to try to make these decisions.

49:03

* Presumably that will be the more and more the future, right, as we understand how to restatify these CIS.

49:16

* Some of them will ignore and say you're fine. Some will need surveillance and some will need to go directly to the operating room.

49:21

* But the better we are at this, the more we can remove things that prevent people from getting pancreatic cancer in the first place, which would be an important thing.

49:28

* And then we talked about, about a number of different risk factors. For the disease.

49:37

* And one of the issues we've run into and we've done a number of studies around this and others have too is that individually none of these right are sufficient, right?

49:44

* You can't set up a program for pancreatic cancer screening. Around smoking like you do for lung cancer, right?

49:52

* The penitence is not high enough and you end up having very poor predictive values because the prevalence is so low.

49:57

* And even when you try to combine these, You don't really get to risk levels high enough, right?

50:03

* If you think we need a risk level higher, a relative risk in the 8 to 10 fold range most likely to simulate what we're seeing in the familiar risk and when you sort of play out the numbers for positive predictive value that's about what we need.

50:09

* You really can't get there either. So really what this has made us start thinking about is other ways to try to define risk, including some of the reverse causation and I'll show you some of that.

50:21

* In a second. But maybe I'll stop for one sec and see if there's any questions or Comments.

50:33

* Yeah, people have questions just raise your hand or just speak up. Specifically.

50:43

* Hi.

50:49

* Or just use it as an excuse to drink some water, but you guys go for it. Yeah.

50:50

* Good.

50:51

* I actually know a question. But. In regards to diabetes. So I know there is an uptick with the use of GLP one agonist, especially like with Gov.

50:52

* Do you think We'll see maybe like a decline. And pancreatic cancer as a result.

51:05

* Yeah.

51:14

* Potentially or do you think there is some unknown long term consequences of using these. Medication.

51:15

* Yeah, that's a great question. I don't know the exact answer. So I think You might suspect, as you said, that If we had ways to Reduce obesity and reduce hyperglycemia that we think are risk factors for this disease.

51:20

* Maybe we would see a reduction in incidents over time. There has been also some concern. That those drugs may actually lead to some inflammation in the pancreas and be a potential cause of pancreatic cancer.

51:38

* There's been a number of studies trying to look at this, which have been not definitive at all, but so I think it we will have to see over time, but I do agree with you that you might suspect interventions that can reduce obesity and diabetes would have a positive effect.

51:51

* And a lower rate. In fact, you know, the rate of pancreatic cancer has increased a lot in the past 10 to 20 years.

52:03

* And some of that has been thought to be due to obesity and diabetes, right? That is playing some role.

52:16

* Because smoking is going down. Right. And so we're seeing less lung cancer, but year over year, substantially more pancreatic cancer.

52:23

* So whatever it is, it's whatever benefit we're getting from a little less smoking is being outweighed by other features, maybe obesity and diabetes among.

52:27

* So it's a interesting question.

52:34

* Thank you. Caroline, you can go ahead and. I see.

52:41

* Yes, hi. Also, I'm in a cafe, so I apologize for the music in the background.

52:44

* But I thought it was so interestingly talking about this link between melanoma and increatic cancer.

52:49

* Do you think it would be? Worth it for people with melanoma to regularly be screened for this gene.

52:56

* That may lead to their system pancreatic cancer.

52:57

* Yeah, it's a great question. So You know, I think and I have to admit I'm not sort of studied that question at all myself.

53:05

* I think it would need to be based on what the prevalence of the gene mutation would be among all of the melanoma carrier, you know, all the folks who develop Melanoma in the US.

53:15

* So my understanding is it's a pretty small number of people with melanoma who have a CDK into a mutation.

53:25

* And so I think at the population level we would need to decide, you know, does that make sense?

53:33

* I think to your point though, of all of the genes on the list. That we talked about.

53:40

* All of them so far as we discussed have really required that there be a family member with pancreatic cancer to do screening.

53:46

* That is actually not been the case for CDC. A because the risk is so high. Even if there's not a family member, those patients have still undergone screening.

53:54

* And in fact, screening has been, if anything, a little less effective in that population because that disease seems to be more aggressive.

54:04

* So what we sometimes see is. They have a CDK in 2 a mutation. We're doing scans every 12 months and they actually develop a cancer 6 months in in between, which is really disappointing and upsetting when that happens because you're trying to screen and you still don't find it.

54:13

* So I think your question is really interesting because I think that is a population that screening we would do.

54:29

* Even if there wasn't a family history of pancreatic cancer itself but i don't know the answer specifically because I haven't really looked at that directly related to melanoma alone.

54:37

* Melanoma is common.

54:47

* Thank you.

54:50

* Alright, so.

54:55

* One more.

54:57

* I was, oh sorry, sorry, go ahead.

54:58

* Okay.

55:02

* There's one more question in the chat. Thank you. I can read it out loud or Maria, if you want to speak up, has there been any surveillance on how 4 month therapy use could either lessen or increase the development of

55:03

* Yeah. There's been a little bit of work on that. You know, women have a slightly lower risk of pancreatic cancer than men.

55:14

* It may be some of the risk factors like smoking and other things may be more prevalent in men, particularly historically, but, but the data have been a little bit mixed in terms of hormone therapy, whether that may reduce or You've made that reduce the risk of pancreatic cancer.

55:20

* There's actually a instructor in, in my group, Anababak who's very interested in that question is in the process of actually doing an analysis around those ideas in the Harvard cohort studies where there's an older study that, Eva Shurnhammer did quite a long time ago.

55:42

* But that was with very small numbers of cases. And so that's now sort of an area that she's interested in, and so that's now sort of an area that she's interested in, again, particularly around some of these.

55:53

* Sex specific differences and incidents and trying to understand why some of that may be, I think is a very interesting question.

56:05

* Alright. Oh wait, hold on, I think I'm seeing one more. Oh, you're welcome.

56:15

* Okay, so let's keep going. Alright, so. The next thing I wanted to talk a bit about was.

56:22

* We've gotten quite interested lately in the idea that There are actually features that the cancer will present.

56:31

* That occur in the time period before the cancer is diagnosed. And if that happens enough in advance and you can aggregate some of these things together, it may allow you to actually pull people out of the population who should undergo surveillance.

56:40

* And so we've gotten interested in these in this. Idea over the past I'd say 5 Maybe 5 to 10 years, for a number of different reasons.

56:55

* One is this is the Yaki Center. This is where we one of the one of the sites we see patients at Dana Farber.

57:01

* And so when you see these patients in clinic, patients with pancreatic cancer, they don't develop symptoms or issues the day before they're diagnosed.

57:12

* Alright, so often what they'll tell you is 9 months ago I had this that happened and 8 months ago I felt like this and 6 months this happened and what you realize is there are a lot of things happening, particularly in the one to 2 years before they're diagnosis.

57:23

* That are probably related to the cancer. But that those things weren't aggregated in a way that told the clinicians that they should look for pancreatic cancer.

57:39

* And that really just comes from listening to patients as you see them in clinic. A second is this is Sir Ashtari who I mentioned before, you know, he has really spent a long time, 20 years trying to think about an elucidate some of the relationships between diabetes and pancreatic cancer.

57:50

* And I think from our own work in that space and Suresh's work, I think what it shows you is again the hyperglycemia is happening at 2 to 3 years in some patients before they're diagnosed.

58:03

* And so again, there's a window there where something is happening that we think is due to the cancer, but they're not diagnosed with cancer.

58:18

* And then we've done a series of studies ourselves together with Matt Vander Hyden's lab.

58:28

* Matt is an oncologist at Dana Farber and, runs a lab at MIT. She's also the head of the Coke Center at the, at MIT.

58:33

* And so we've had a series of papers over about the past 10 years. Where we've gone back and forth between people and mouse models and shown that there again are a lot of changes happening in both before cancer is diagnosed and that this may provide a window for diagnosis.

58:41

* Early. And really what I'll show you is where this ends up going. Is the idea that we could combine some of these features together with risk factors in sort of higher order models to allow us to pull people out of the general population and I'll show you a manuscript we published recently around these ideas.

59:00

* So if you think then about pancreatic cancer risk, yes, there are risk factors. And then there are a bunch of cancer associated features.

59:20

* And as you start to aggregate these things together, you realize there are quite a number of these features that are occurring in the one to 2 years before diagnosis.

59:26

* These can be symptoms, right? Things that people are telling you. But again, people often have abdominal discomfort from pancreatic cancer.

59:35

* That doesn't happen the day before they're diagnosed. That can happen many months before. They can actually have issues with their diet, including changes in their food preferences, malabsorption, because one of the jobs of the pancreas is to make enzymes to absorb food.

59:42

* Again, we talked about new diagnosis like diabetes. It's also the cancer that really has among the highest rate of Venus thromboembolic events like Venus, the leg being the most common.

59:56

* I'll show you a study we did that some of this you can aggregate into changes in medicines that people take and that actually has predictive ability.

1:00:09

* Lab changes, imaging features. So really there's a wealth of information, particularly as medical records have become digitized.

1:00:17

* And we're putting all of this stuff into the medical record. There's really a lot of information here that maybe allow us to take what we learned and talked about over here.

1:00:25

* And added together to come up with a way to find people at risk. So we did a couple of proof of principal studies around some of these ideas.

1:00:35

* I thought I'd just show you a couple. This one was done by Ian Zhang, who's, a PhD student working with Ed now, who actually worked a bit with us prior to starting his PhD.

1:00:43

* And what I, in wanted to do, which I thought was a really interesting study is, you know, there's again lots of data in the medical record and one of the things that has become very structured in the medical record as medications.

1:00:53

* Right, whenever we write medications now, they took away our prescription paths, right? When I started, I would just scribble something on a prescription bed and hand it to the patient.

1:01:06

* And then a bunch of years now they like forcefully removed it from my hand and wouldn't let me use that anymore.

1:01:14

* And so now in order for me to write a medicine, I can only type it in the medical record, right?

1:01:19

* So every medicine goes into the medical record. The dose is known the day it starts is known, the day gets refilled is known.

1:01:24

* So there's really a lot of information. So we decided we would do a proof of concept study using a couple of the Harvard cohort studies and the nurse's health study and health professionals follow study where some medication data has been collected and in some instances that medication data can be collected every 2 years.

1:01:29

* And you could actually ask. Over each 2 year period over time, what change did people make in their medicines?

1:01:50

* And so if you ask and say the questionnaire started here and then 2 years later, 4 years later, 6 years later, and then they got their cancer diagnosis here, time 0.

1:01:52

* What happens if we went back to the last questionnaire? That they had before their cancer was diagnosed.

1:02:08

* And the one before that. Right, so on average, that's about a year before their cancer is diagnosed.

1:02:15

* And 3 years before their cancer is diagnosed and then ask what changed. Right, what medications did they take differently, either starting a new medicine or stopping a medicine?

1:02:20

* And we went in with a few hypotheses about what medicines we thought people would start and stop.

1:02:30

* And then what you did is ask, well, could this predict risk of pancreatic cancer in the next 2 years.

1:02:36

* After you see what medicines they changed. And the answer was yes, and I'm just gonna present you one, you know, one figure from this, but in particular, as we just talked about, if you newly started diabetic medicines, medicines for diabetes, particularly insulin since the diabetes that people get related to pancreatic cancer in a year or 2 before is often rapid.

1:02:43

* meaning their sugar goes up very quickly. Much more so than often you see sort of in standard run to the mill diabetes and they get more hyperglycemic.

1:03:05

* So it becomes harder to control and these patients more commonly end up on insulin. So starting of insulin was one, although any diabetes medicine actually predicted risk.

1:03:14

* Anticoagulants like we just talked about these patients are at risk for clots and sometimes the clot actually precedes their diagnosis of cancer.

1:03:24

* And then there are weight changes and what we see in clinic is that patients often have stopped or reduced the doses of their anti hypertensive medicines because those are often in place because they were somewhat overweight.

1:03:33

* Which raised their blood pressure. And you could start to make a matrix of medication change and say, well, if they start this one and stop this one or what if they start and stop both of these and you can start to see that this actually predicts risk.

1:03:41

* In an unadjusted sense if they had a couple of these different changes upwards of 5 fold.

1:03:58

* And if you adjust for some of the other risk factors, we already know more like threefold. But this started to clue us in.

1:04:03

* Again, that there's a lot of latent data in the medical record that could be useful in predicting risk.

1:04:10

* That's not causation, right? It's not that the antiquated medicine is causing their cancer.

1:04:16

* It's an effect, right? It's the reverse causation and that that may be useful. Then we did another study.

1:04:21

* In this one we were looking actually at CT scans. This goes back a little bit to Laura L's question, where we were actually taking CT scans from people before their time of their pancreatic cancer diagnosis actually was a similar design to how Suresh Chari did.

1:04:27

* One of the studies that I mentioned. And this is actually a study we did together with Michael Rosenthal, who's a study we did together with Michael Rosenthal, who's a radiologist.

1:04:46

* At the Brigham and Dana Farber. And also a computer scientist. And so what we did is we made, AI algorithms, machine learning algorithms, to take a CT scan and be able to, in an automated manner, segment all the organs in the ab, right?

1:04:53

* Not all, many of the organs in the. So for example, The yellow is the liver.

1:05:09

* So ground truth means we had a radiologist go through and segment it, meaning they went through the images and pixel by pixel on the images said, liver, liver, liver, this is liver, right?

1:05:16

* And that's colored yellow. And then we trained the computer to basically do that. And then what you can see is the prediction is what the computer says is liver.

1:05:26

* And the ground truth is what the person initially said was liver. And then we went through and systematically did this for a lot of different, markets.

1:05:36

* Liver, spleen, pancreas, kidneys. And some others. And so what you could start to do with that information was start to ask well what's the distribution of these organs in the general population and then what happens in the time before someone is diagnosed with pancreatic cancer.

1:05:44

* So in this paper, what we did was actually skeletal muscle. We quantified skeletal muscle on the CT and also fat, so adipose tissue.

1:06:04

* And this was based on some of the work we had done with Matt Vander Hunt's lab in the past where what we had seen both in mouse models and some preliminary data in people is that it seemed like As people were getting closer to their time of pancreatic cancer diagnosis, they were wasting skeletal muscle and also adapostic, mean they were losing them.

1:06:13

* So what we did then is ask, what was that in the population? Across entire population by age and sex and race and created essentially, standard curves for what that should be if you were a particular age, a particular sex or a particular race.

1:06:32

* And then together with Anababic I mentioned before, looked at CT scans from before diagnosis and patients with pancreatic cancer and match controls who do not get pancreatic cancer.

1:06:49

* And what we could show is that as you get closer to the time of your pancreatic cancer diagnosis, which is this direction.

1:06:59

* You see that the skeletal muscle, this is showing muscle that we see somewhat similar things with, adipose tissue.

1:07:07

* That the amount of skeletal muscle goes down. And what we can show is that, again, there are these differences happening in patients before their cancer is diagnosed that are actually detectable either by seeing say patterns and medication use.

1:07:14

* Or patterns on CT scans and that these may be useful. And that then takes us to sort of some of the next steps.

1:07:30

* So one of these is now to use the electronic medical record. And machine learning models that tries to take into account all this information, right?

1:07:37

* Feeding this different information to then predict who's going to get risk of pancreatic cancer.

1:07:47

* In the first paper doing this that we published was last year together with chisander who's at Dana Farber in Harvard medical school and Sauron Brun who's in Denmark.

1:07:49

* And we started out somewhat simpler. This was a just using ICD codes from the medical record.

1:08:04

* So as folks who are more clinical may know every time we see a patient in clinic, you have to bill for the visit, right?

1:08:11

* So you have to say you did XY, and Z and that's why the insurance company should give you a hundred bucks for whatever you just did.

1:08:17

* So to do that, you have to put a code, which is a international, disease code, ICD code.

1:08:25

* That says what the diagnosis were that you were treating. And so it turns out you have millions and millions of these codes sitting behind the medical record for all of the visits that people have had.

1:08:32

* And that this ICD code structure as it gets changed over time has become more and more complicated. And so there are now tens of thousands of different codes.

1:08:45

* So the question of this study was, could you take these codes? Look at them over time in relation to both each other and the diagnosis of pancreatic cancer and predict who's at risk for pancreatic cancer in different time frames and we chose a number of different time frames.

1:08:54

* I'm a what I would say is this, to a degree actually worked. In fact, work better than I think we suspected that there is now just a tremendous amount of information in the medical record.

1:09:12

* And you can start to leverage this. Ideally where we would like to go for early detection, right?

1:09:24

* You pick out again an individual who's at risk for the disease in the next year or 2 years.

1:09:30

* That relative risk is high enough that it justifies doing an MRI or an which is where this is heading in the follow up studies that we're working on now are trying to incorporate lots of other types of information.

1:09:36

* This was sort of the initial proof of principle with ICD codes, but now using lab tests and medications and blood.

1:09:49

* I just said that test blood tests, imaging, other things, to try to help us put this together.

1:09:57

* Then the last part to this I just wanted to say. Is you can also think about this beyond a single disease, right, beyond pancreatic cancer only.

1:10:03

* And so we got interested in the idea that weight loss can be seen in other cancer types, not just pancreatic cancer.

1:10:12

* And could you use this as a way to again pull people out of the population who should undergo some sort of cancer screening.

1:10:20

* I mean, this was a study that Charlie Wong also worked with and also now works with us as a post-doc did that was just published recently if you're interested in reading more where she used weight change again in the nurse's health study and health professionals follow up study to actually predict risk of cancer in the next year.

1:10:21

* It's not causation, right? It's not causing the cancer. It is a consequence of the cancer.

1:10:48

* But it turns out there are some cancers that do this and many cancers that don't. And when patients come to clinic to see their doctor, seeing that their weight has changed could be a signal that a cancer is coming in that a further evaluation should be done.

1:10:53

* And she explores a number of ways to try to do that in the management. Alright, why don't I stop again for a second?

1:11:08

* See if folks have questions and then I don't think there's too much more time left. I may have to go quick through the rest.

1:11:17

* If you remind me how long this goes.

1:11:23

* Yeah, it goes until 3 30. So you have 18 min.

1:11:25

* Okay, all right, not much. Other questions folks have or anything we should discuss before I'll quickly go through the rest

1:11:28

* I have a good question. Oh, sorry. Go ahead, Jen.

1:11:37

* Hi. Okay, thank you. I want to ask that could medication and behavioral risks such as smoking or weight change and obesity, increase the expression of the mutated.

1:11:38

* So let me just see if I understand. So you're asking. People who smoke or, are the mutations in the tumor different or do they synergize with inherited mutations to cause the cancer?

1:11:52

* Or neither if I didn't get it right. And either one of us. Okay.

1:12:05

* Yeah, like in inherited things because like, obesity actually puts our body in a low rate inflammatory state.

1:12:06

* So that could I alter the micro environment and alternative gene expressions.

1:12:14

* So yes, so there's been some really interesting work. Mostly in mice that have tried to understand why obesity is a risk factor, molecularly for pancreatic cancer.

1:12:21

* And one of the most interesting studies show that there's actually interactions between the epithelial cells, the acider cells that make the enzymes.

1:12:35

* In the hormone producing cells. Alpha beta cells in the pancreas. And obesity changes the communication.

1:12:45

* And in the setting of obesity it actually has a signal that originates from some of the alpha beta cells that essentially promote it's almost like the repair and growth response within the asthma cell compartment.

1:12:55

* So, yes, I would say you're, I would totally agree with you that. Obesity is working by some mechanism, right?

1:13:13

* It is doing something within the pancreas that's causing this and that you can decide for that at the molecular level.

1:13:20

* Thank you.

1:13:28

* Hey there, are you just had a quick question about the, the slide that you're just on about the predictive modeling or booking.

1:13:31

* Do you know if the top of your head what algorithm seem to predict. The best

1:13:38

* Yeah, so. We used actually a number of different machine learning models. Which you can go to the paper to see this specifics.

1:13:45

* You know, ultimately I think, we needed a, we needed models that took into account time series.

1:13:48

* So I think one of the advances of that paper and I'm not a computer scientist, so this wasn't me and my specific insights, but I think one of the advances of that paper was that it wasn't just the ICD codes you had.

1:14:03

* It was actually the order in which you had them and the timing in which they related to one another. And so the transformer models were some of the best for that that took into account not just what codes were there, but the time in which they developed in their relationship with one another.

1:14:18

* And Laura, I mentioned this actually in her question at the beginning, which we had a study a few years ago.

1:14:35

* That the new onset diabetes that happens from the cancer when it's paired with weight loss the risk of pancreatic cancer goes up dramatically.

1:14:41

* Either one alone has less risk, still some risk, but less. And so I think those types of studies will show you that it's the combination of factors that are happening.

1:14:48

* And we can see that in these models because you can see that some of these factors are going together within the model to increase risk.

1:15:01

* So, but certainly if you have, you know, more interest in the actual models, the paper goes into quite a lot of detail describing the different models that were used.

1:15:11

* Cool, super interesting. Thank you.

1:15:20

* Yeah. Alright. So let's see, we made it through the first bullet point. That wasn't very good.

1:15:23

* Prediction of timing on my part. So let's let's go relatively quickly through the rest.

1:15:27

* Alright, so I'm gonna skip that. Let's skip some of this stuff.

1:15:36

* Let's talk a little bit more about this. Cause I think this is relevant to what we talked about.

1:15:42

* So again, there are a number of symptoms that people get from this disease. We talked about a number of these because now we're really thinking about how to leverage them for earlier diagnosis.

1:15:46

* These are things like weight loss, early satiety where people can't eat as much at one time.

1:15:56

* They can get nausea or vomiting or upset of their bowels. One of the things we've been studying a lot is how pancreatic enzyme secretion, which is what breaks down the food in your bowel, goes down in patients who have an early tumor.

1:15:58

* And this is now something we're leveraging to try to again try to find these tumors early.

1:16:15

* But there are these symptoms that can occur. Anyone individually may not tell you there's a cancer, but as you start to think about biologically how they go together, I think can be useful.

1:16:20

* Signs means what the doctor can see, right, when they. When they examine the patient.

1:16:31

* These are usually later. Stage stuff, right? So once you can feel, say, a It's not usually a good sign, right?

1:16:40

* These are usually things that are a bit later in terms of the development of the cancer. I think more helpful is going to be some of the symptoms that we describe.

1:16:47

* And then these patients all get sort of a standard workup, including CT scans. They may get the endoscopic culture son that we talked about because you also can buy up see the tumor that way.

1:16:56

* I mean, ultimately you need a biopsy where you must buy up to either the tumor in the pancreas or the metastasis to define what's going on.

1:17:06

* And then you can stage these tumors, which we talked about, right? So there's more limited stage or stage one and 2.

1:17:14

* There's what's called locally advanced stage 3 and stage 4. They sort of fit into these 3 categories.

1:17:17

* Which we mentioned at the beginning. And then we talked about this fact that there's so few. Right, who have localized disease at diagnosis that this really is something that we need to be working on, to change.

1:17:23

* And not only do 80% present with advanced disease. Alright, either metastatic or locally advanced, but among those 80% the median survival is quite short, right?

1:17:39

* So it's less than a year. I'm and again that goes back to what we talked about at the beginning that there aren't that many effective therapies.

1:17:51

* So again, it really highlights the need to find this disease earlier. Alright, so I'll just spend a couple of minutes then on how we manage the disease.

1:17:56

* I would Very much say that as you guys. Study particular cancers that you really learn how those cancers are treated and how patients experience those cancers.

1:18:01

* That you know, you are fortunate living in Boston. There are a lot of really good cancer centers in Boston and there's a lot of oncologists.

1:18:17

* And so really trying to spend some time either collaborating with an oncologist who treats the disease you're interested in.

1:18:25

* Or even spending some time in clinic, I think is important because it really helped you. Understand the disease you're trying to, do research on and also what patients go through.

1:18:32

* So I'm gonna skip this part. Let me do. Let's do this.

1:18:45

* Why don't we just talk about one patient just to give you a sense of that? And then I think we'll finish.

1:18:51

* So this was a gentleman who I took care of. It's a 53 year old guy.

1:18:56

* He had a couple of respectors like we talked about, he was overweight. Definitely smoked and drank a bit too much.

1:19:02

* And actually in one of those episodes when he was doing a little bit of that too much he actually fell and he broke his ankle.

1:19:10

* And when he went to go get surgery, orthopedic surgery to repair the ankle.

1:19:13

* They saw that his liver tests were abnormal. And he did not at that point have symptoms of a pancreatic cancer per se, but they notice that his liver tests were somewhat off.

1:19:21

* And because of that, they then did a scan to try to figure out, well, what's going on with his liver.

1:19:31

* They did an abdominal scan and they actually saw a mass in the pancreas. It was only in the pancreas.

1:19:33

* There was not cancer and other organs. He had some evidence early evidence of obstruction of the bile duct and had a procedure to open that.

1:19:41

* And then he had the ultrasound we talked about to biopsy the mass. And that mass was add no carcinoma.

1:19:51

* And I know carcinoma is between 90 and 95% of pancreatic cancer.

1:19:57

* As you guys know, it's a histologic description of a gland forming tumor.

1:20:02

* We always do a special kind of CT scan for pancreatic cancer called a pancreas protocol CT.

1:20:06

* That's what helps us do surgical planning to make decisions. And I'll show you his scan in a second.

1:20:12

* But he had a 2 cm mass. In the pancreas. That's actually top level.

1:20:17

* Size for a T one tumor. Right. So the small tumor. But it abutted a couple of the veins that run near the pancreas.

1:20:23

* We had to put in a port, which is an IV that goes under your collarbone.

1:20:31

* It's semi permanent. It can come out, but it can also stay in for years if you need it.

1:20:35

* And we started him on. Chemotherapy right away. He got 2 months of chemotherapy.

1:20:40

* We shrunk the tumor and he went for surgery. This is a whipple procedure which is as folks may have heard as a large complicated kind of surgery, definitely a surgery you want done in a big.

1:20:45

* Economic center where they do hundreds of these a year, not a small place. And again, he fortunately had a small tumor.

1:20:54

* He had no lymph nodes that were positive. We gave him 4 more months of chemo because 2 months is really just not enough.

1:21:04

* To get rid of this. Disease with the hope that by doing this, we would cure him, right?

1:21:06

* So this is just what we see and it goes back again to some of the points we talked about. That this tumor is not easy to see.

1:21:16

* This is the tumor. Right here that I'm circling if you can, I hope you can see my pointer.

1:21:21

* I mean the yellow is the era. Right, and then this is the vein that it's up against, the superior Mesenteric vein is right here that's the bright.

1:21:24

* Sort of blob. And that's the tumor. That's what was biopsyed and shown to be cancer.

1:21:36

* This is something we see a lot of, which is that early on with early tumors, you see dilated pancreatic ducts, which is this dark stripe.

1:21:39

* In the middle of the pancreas, the rest of this sort of fish shape thing is the pancreas itself.

1:21:49

* This is part of what some of these machine learning algorithms are picking up is that you see this dilated doctor early on.

1:21:56

* And then just as comparison, this was the tumor again here. And then after we gave 2 months of chemotherapy, you can see it's largely gone, right?

1:22:03

* This is the stent. This circle thing that's propping up the bile duct. But you know longer see that tissue, that dark tissue here next to the vein.

1:22:12

* Okay. So that was great. And we really hope he was going to be cured and he was for a while, but his tumor eventually did come back, unfortunately.

1:22:22

* And he developed a new lung nodule, in 2,018, so this is now 3 years.

1:22:26

* You have 3 years, we had no cancer. Because he's a long term smoker, we actually did surgery to remove it because we had to make sure it wasn't lung cancer.

1:22:36

* And it wasn't, unfortunately, was his pancreatic cancer. We're able to wait another year actually before many new ones showed up.

1:22:44

* And then eventually had to give him chemotherapy and he was on chemotherapy for about a year, before he passed away.

1:22:52

* I mean, we didn't really talk about this much, but we now sequence the DNA in the tumor in every patient.

1:22:59

* We look for a number of different characteristics. And we did sequence to look if he had any inherited mutations because all patients should have that done.

1:23:05

* And just to give you a sense, this is a chess CT scan. Some of you are probably quite familiar with this, but this was his initial recurrence in 2,018.

1:23:12

* This is the recurrent lesion. All of the black is the normal lung.

1:23:20

* In the middle is the media style. And this is the, the great vessels in the Media Steinem.

1:23:26

* But this is the one we removed by surgery because we weren't entirely sure what it was.

1:23:32

* And then this a year later are the recurrences. This is another nodal in the long.

1:23:33

* This is another one here. And then eventually he had more and more. That grew and ultimately he passed away because the disease.

1:23:42

* Became refractory to chemotherapy. Alright, why don't I stop there?

1:23:50

* Maybe I'll just say again in summary and then try to have a couple of minutes, at least we can.

1:23:56

* Have other questions but. Tough disease, right? Third most common cause of death from cancer in the US.

1:24:02

* Really I think prevention and earlier detection are really important. Right to try to improve survival from this disease.

1:24:05

* It's hard, right? Early detection is a hard problem. But there are now, I think, a number of avenues that are moving forward to try to do this.

1:24:14

* We talked about risk factors including smoking, obesity. Obesity, diabetes, pancreatitis.

1:24:25

* We talked about, and then family history. We did a little less discussion about treatment, just given time.

1:24:32

* But the patient I showed you is sort of a, an example of trying to use chemotherapy and radiation or chemotherapy and surgery to try to cure the tumor.

1:24:39

* And then trying to treat it as it recurs. And then genetic testing is now recommended for all patients with pancreatic cancer for the reasons we describe.

1:24:47

* And then we didn't talk much about this today, but ultimately we do a lot of clinical trials at Dana Farber where we're testing new therapies or testing new detection approaches.

1:24:57

* We have a new trial we just open for patients that have familial risk. Trying to use these new multi-cancer early detection tests with sulfur DNA to try to see if we could do better by using that in addition to scans.

1:25:08

* And ultimately it's really only by doing these trials, right, by trying new things and having sort of patients be willing to try those things with us that we make progress.

1:25:22

* So. I don't know, I stop and I'll stop sharing and thanks for everyone's attention.

1:25:31

* Thank you. Let's open it up for any, comments from, our students.

1:25:38

* I have a question that, When it comes to understanding those pictures that or shown, the cities can.

1:25:46

* Are we supposed to as public health children? Are we supposed to understand them?

1:25:56

* I'm certainly not going to tell you what you need and not need to understand, but I would say I show you that more as just so you see what clinicians are looking at less that I would.

1:26:01

* Expect if you have no medical training that you're supposed to be able to read a CT.

1:26:11

* Okay, thank you.

1:26:16

* Right, I wonder just in terms of the descriptive epidemiology, and looking sort of where pancreatic cancer has been rising.

1:26:20

* It feels like it's popping up even more so in women than men, even though men still are at greater risk.

1:26:26

* I wonder what your general thoughts are in terms of. Is that a real thing? Our pancreatic cancer is also vulnerable to sort of this earlier onset that we're seeing for other GI cancers, but just if you talk a little bit about the genetic epidemiology.

1:26:35

* And what you see in clinic too.

1:26:47

* Yeah, so it definitely does seem like pancreatic cancer is increasing in young people. You know, in some ways not too dissimilar from colorectal cancer, although the prevalence of pancreas is obviously lower.

1:26:54

* And that now has been shown in actually multiple studies in multiple countries that that is true. You're right that some of those data, not all, some have suggested that some of the increase in younger individuals is more in women than in men.

1:27:09

* You know, in clinic, actually I've been seeing that a lot. Lately. I would say over the past couple of years, I have now been pretty routinely seeing patients in their thirties and forties with pancreatic cancer, which I just I can't remember that 15 and 20 years ago.

1:27:30

* I mean, maybe I did, but I don't really remember that the way I'm seeing it now.

1:27:48

* I had I had a stretch a few months ago, right? I met 3 people in their thirties in 2 weeks.

1:27:53

* And that's just not normal. That's just not the way it used to be. So something is, I think, different, you know, in terms of what's happening.

1:28:00

* You know the ideology of that's not that clear right why exactly that is just like in colorectal cancer it hasn't been so clear either.

1:28:10

* I think we did have some work and others have shown this to that. There does seem to be. When you have these risk factors, they do seem to matter more in younger individuals than older.

1:28:17

* That if you're obese or you smoke, that it increases the relative risk of cancer at younger ages more so than at older ages.

1:28:29

* Right, still the overall prevalence is much higher as you as you age. And we've actually been doing some work looking at this now trying to understand that by actually looking in tumors.

1:28:37

* And trying to see how age related mutation patterns differ. Compared to risk factors that you have.

1:28:48

* Because there are ways to find signatures in the tumor itself that tell you what's own was exposed to.

1:28:56

* And that's part of the problem is it can be hard to see in the tumor, you know, did the obesity as that really interesting question one of the students asked like, oh, how's that actually working?

1:29:02

* Right? Why is obesity related to risk? We can start to do this with some risk factors by understanding the tumor and trying to find signatures of what they were exposed to that led to that tumor to develop.

1:29:07

* But I think at this point, I don't really know the answer aside from it does seem like obesity diabetes do matter more when you're younger.

1:29:27

* And that that may be what's in part playing a role. And then there may be other exposures we have that we don't know yet.

1:29:33

* Great. Thank you so much. Any other final comments or questions?

1:29:41

* Yeah.

1:29:47

* I got a final question. Doctor, do you think, or what do you think is the importance of the familiar pancreatic cancer syndrome?

1:29:48

* And surveillance. And high risk patients for pancreatic cancer screening.

1:29:54

* D the importance meaning should we do it or maybe tell me a little more what you mean.

1:30:01

* And more in terms of the number of patients, the, first, patients, or formulas that actually have the disease.

1:30:06

* For instance, we know that familiar. Cinder is more than 2. Should we, should we keep these number, this threshold number or probably, should we reduce it?

1:30:15

* Do you have a comment about that?

1:30:27

* Yeah, and when you say 2, you mean the number of relatives in the family. Just trying to make sure I answer your question.

1:30:30

* Yes, correct. Yes. Yes.

1:30:36

* I see. Huh. Okay. Yeah, so, you know, so far from the studies that have been done, it looks like people who have Just one first degree relative have a pretty modest increase in risk, a relative risk more around the 2 to 3 range.

1:30:38

* Which seems not to be sufficient to recommend screening. So right now, people have one first degree relative are not being recommended for surveillance.

1:30:53

* Unless they have a genetic mutation that they inherited. Right, so if they have one first of your relative that relative had a BRCA 2 mutation and they inherit that PRC 2 mutation, then the risk is much higher because the penitence is much higher when you have not just one family member.

1:31:02

* But you actually have a known genetic event that's predisposing the family to get the disease. So in that circumstance, we would recommend it.

1:31:18

* You're right. That in families that have multiple relatives. But don't have a known genetic mutation.

1:31:27

* The exact cut point at which to say you should do surveillance is not that clear. We generally now will recommend people who have 2 or more.

1:31:35

* First degree relatives in the family with pancreatic cancer that all of the first degree relatives around them Get screened.

1:31:45

* And that's because the relative risk seems more like it's in the 5 to 6 range, which is higher.

1:31:52

* And seems more appropriate. However, there have been a couple studies that have shown If you look at people who have a genetic mutation in their family and you look at those who just have the familiar risk.

1:31:56

* The penitence is clearly lower among those that have 2 family members and no genetic mutation than those that have even one family member with a genetic mutation.

1:32:12

* And so there continues to be debate as I think you're alluding to. About whether we should be using family history alone.

1:32:22

* Without a genetic mutation. At this point we still do and those people still qualify for these.

1:32:29

* Problems and trials that, that we are doing. But I think my last part would be I think the way you're thinking about it is exactly how I think about it too, which is what's the risk level?

1:32:31

* At which surveillance would be appropriate. And then what are all the different ways you get to that level? Right, I don't really care, right?

1:32:48

* If it's these 2 things or these 4 things that get you to a risk level, great. If it's these one or 2, fine.

1:32:56

* But it's really trying to define risk in a way that can be clinically actionable. That's important.

1:33:02

* Well, thank you so much, Brian. This has been really amazing and, This is just, yeah, thank you again.

1:33:11

* Let's give Brian. Our, thanks and wish we could have been in person but great to see you.

1:33:18

* ExcellentThank you

8

* Just

0:06

* okay.

0:12

* Kresge 502 Cart: Oh, whoops! Go back to the zoom. Alright

0:16

* Kresge 502 Cart: good to see you all. We just wanted to start today to quickly talk a little bit more about the assignment. Hopefully, you've all had a chance to review the document in detail, and you've been meeting with the group component. But both components, the individual and the group component are due on Tuesday, individual component, due at 1159 next Tuesday.

0:55

* Kresge 502 Cart: and the group component, regardless of which day you're presenting. The slides are due on Tuesday. Just so. Everyone is due at the same time. But we did put up the schedule, so you should all know and be prepared.

1:19

* Kresge 502 Cart: What we're looking for. We just wanted to quickly outline for the individual. Write up truly what we're looking for is this list here. So just making sure kind of checking off as you're going through and writing this all up in your own words, using these databases to get at the descriptive epidemiology and kind of checking off each of these individual components. This should be doable in 2 pages single-spaced, but we do give you a little bit of wiggle room if you

1:36

* Kresge 502 Cart: want up to an extra page that's totally fine, but you should be able to do it in 2 pages single space without any worries.

2:04

* Kresge 502 Cart: Anything to add. Michelle. Well, I mean, does anyone have any questions concerning the individual write-up

2:12

* Kresge 502 Cart: is 2 pages the minimum, or would have less

2:23

* Kresge 502 Cart: if you can do it, unless sure as long as you're hitting all of these points that we've outlined. That's great. If you do it in less than 2. That's awesome. Yeah, we've had. Previously the assignment was 2 pages, and we asked, people were asking for more room. So we're being flexible, and you can have more room. But you can definitely do less. So yeah.

2:29

* Kresge 502 Cart: any other questions

2:53

* Kresge 502 Cart: cool. And then for the group part, hopefully, everyone has met with their teaching staff member and talked about your risk factor. But if you have any questions you can reach out to Michelle or I, and happy to chat

2:58

* Kresge 502 Cart: anything to add up about the assignment.

3:12

* Kresge 502 Cart: Then see, you guys, on Tuesday for your first group presentation. Awesome.

3:20

* Kresge 502 Cart: Alright yeah, slip should hit her head. She's fine, but she won't be in class today.

3:30

* Kresge 502 Cart: But there was a nice write-up. She did a nice interview of the Harvard Magazine, so I think we put an attachment on it.

3:42

* Kresge 502 Cart: Course websites react to one.

3:53

* Kresge 502 Cart: So that's a very nice thing to do. So it's my pleasure to introduce heather.

3:57

* Kresge 502 Cart: Heather has been really like a world leader in the epidemiology of breast cancer.

4:19

* Kresge 502 Cart: She's Pi, the principal investigator nurses, one and 2. So I had to lead credible cohorts, and she said, so much work, a lot of different areas, but a lot of it, hormones.

4:30

* Kresge 502 Cart: the etiology of breast cancer, but also a lot of depression options, carbon nutrition. So she really does really a world leader in this project. So we're really

4:50

* Kresge 502 Cart: pleased to have her get this talk

5:02

* Kresge 502 Cart: because you've been doing this at 5.

5:06

* Kresge 502 Cart: Something like that. Yeah, he took this course. Oh, yes, many, many years ago

5:08

* Kresge 502 Cart: I was, gonna say, Graham, but he talked cancer prevention desktop and then go full should work, or I can just share

5:19

* 6.

5:40

* Kresge 502 Cart: Okay, let me stop sharing. Just

5:41

* Okay?

5:50

* Kresge 502 Cart: Oh, no. But you know what I did want to share my desktop, because

5:54

* Kresge 502 Cart: sorry

5:58

* Kresge 502 Cart: you'd think, after all these years of the pandemic, I would not have exactly what to do.

6:07

* Kresge 502 Cart: All right. So that's working on the screen working on. Zoom, I'm going to minimize this

6:14

* Kresge 502 Cart: perfect. Thank you. All right. Welcome, everybody. Nice to see you all here today and looking forward to talking a little bit about breast cancer today

6:24

* Kresge 502 Cart: and feel free to jump in with questions. I'm going to ask you some questions as we go along, and I would love to hear your thoughts as we're proceeding with this. So first, I'm going to start with a question for you.

6:39

* Kresge 502 Cart: So if you. Go to this QR code and I would love to hear you can put in just a risk factor for breast cancer that comes to mind for you.

6:55

* Kresge 502 Cart: And once you all have the QR code down, I'm going to switch screens here

7:07

* Kresge 502 Cart: when you get it.

7:22

* See a couple more phones up. Okay. So now I'm gonna see if I can swap over to

7:25

* that

7:31

* Kresge 502 Cart: this one awesome.

7:33

* Kresge 502 Cart: So I'm seeing Brca gene adaposity, obesity. childhood obesity, family history, mela parity

7:38

* Kresge 502 Cart: brackle, one genetic. Yeah. Age smoking. Calvi 2.

7:49

* Kresge 502 Cart: ATM,

7:56

* Kresge 502 Cart: yeah, definitely got some genetic focus on here. Great

7:58

* Kresge 502 Cart: family history. estrogen, postmenopause.

8:02

* Kresge 502 Cart: Great. All right. Well, we're going to talk about a lot of these today, and if we don't talk about them, and you have questions about any of these that you've put in, or that others have put in, feel free to bring it up. This is awesome, wonderful, thank you.

8:09

* Kresge 502 Cart: Great. So just as an overview, we'll go through a little bit of descriptive and epidemiology, and then go through risk factors thinking about how risk factors or breast cancer occur across the life course, focus, start on early life. Think about reproductive factors.

8:23

* Kresge 502 Cart: how endogenous hormones fits into this and underlies a lot of the risk factors risk factors that are modifiable or potentially modifiable, and then talk about mammographic density risk prediction. I actually took out because I didn't think we would have enough time as well as the subject. So sorry about that. I left those in the overview side by accident. So in terms of descriptive epidemiology.

8:39

* Kresge 502 Cart: I actually have another poll. So racial disparities in breast cancer exist, and which of the following best describes this disparity. So again, I'm going to swap screens, and I think you can still get the QR code if I go to the second question here.

9:03

* Kresge 502 Cart: So the it's a little hard to read here, but the options are the first one. Black and Hispanic women are more likely to be diagnosed with breast cancer than white women.

9:18

* Kresge 502 Cart: Second, one is black. Women are more likely to be diagnosed with breast cancer and to die of breast cancer than white women, the third, although white women have the highest incidence, rates of breast cancer. Black women have the highest mortality rates

9:28

* Kresge 502 Cart: the fourth black and Hispanic women have higher breast cancer mortality rates than white women. So see, see what you think about this.

9:41

* Kresge 502 Cart: and then we'll go through a bit of the descriptive epidemiology. So right now we have most people saying the third option. So although white women have highest incidence rates, black women have highest mortality rates, and a couple of people showing black and Hispanic women having higher breast cancer, mortality rates than white women.

9:50

* Kresge 502 Cart: others.

10:16

* Kresge 502 Cart: All right. So we'll go through some of the descriptive epidemiology and see what the answer to this question is.

10:19

* Flip back to Powerpoint here. Okay, so thinking about, I'm sure you are all familiar with global maps like this, looking at incidence of cancer across different countries around the world. And what you can see here is that the rates of breast cancer do vary quite a lot across different countries. And so what is something that you notice about this with a darker blue showing higher incidence, rates of breast cancer.

10:25

* Kresge 502 Cart: Sorry more towards the high income countries, high income countries. Right?

10:58

* Kresge 502 Cart: Yeah. And so, any ideas about what might contribute to that.

11:05

* Kresge 502 Cart: Why might we see this pattern

11:10

* Kresge 502 Cart: more screening? That's an interesting point. So more screening might be detecting more cases of breast cancer.

11:17

* Kresge 502 Cart: What else? What else might differ

11:26

* Kresge 502 Cart: obesity, obesity. So thinking about patterns of risk factors could differ across the countries as well as patterns of screening

11:30

* Kresge 502 Cart: anything else.

11:40

* Kresge 502 Cart: I mean.

11:47

* Kresge 502 Cart: less developed countries

11:51

* question.

11:55

* Kresge 502 Cart: They die younger. You do other causes rather than developing cancer. Infectious causes.

11:55

* right? So potentially that shift between communicable diseases having a bigger impact and then noncommunicable diseases. Right? So but some of the things that you're all getting at are the fact that there are things other than genetics that differ. So there are different patterns or risk factors which leads me in in my interest in breast cancer. To think that maybe some of these differences are factors that are modifiable so that we can think about how to reduce rates of breast cancer and prevent breast cancer.

12:04

* Kresge 502 Cart: So the other factor that we can see plays into this. It really highlights that it's not all genetics being the difference. This is quite an old study, but it was really an interesting way of looking at how rates of breast cancer change with immigration. So, looking at the lowest.

12:34

* Kresge 502 Cart: her are Japanese in Japan, and then looking at Japanese immigrants in Hawaii and in San Francisco compared to the top, solid red being whites in San Francisco. And so you can see that as people move and spend more time in this country they end up adopting the rates of the higher incidence rates of the whites in the country, which again leads us to think that it's not genetics

12:53

* Kresge 502 Cart: that genes don't change this quickly, but it has to be something about the environment, lifestyle, or changes in reproductive patterns that could be contributing to these differences here.

13:18

* Kresge 502 Cart: So if we look at the age, standardized incidence rates across the world, you can see here the incidence and mortality this is ranked by instance. And again you can see patterns of the more

13:32

* Kresge 502 Cart: Westernized countries at the top with a higher incidence rates. But then, when we look and rank it by mortality rates, you can see a shift in countries. And so this is a pattern that is probably similar to looking at other cancers as well, that there's a difference in the mortality patterns across the globe.

13:49

* Kresge 502 Cart: So you can see when we look within the United States that breast cancer ranks as the highest incidence cancer, in the in females, and it is ranked second in terms of the number of cancer deaths that it causes and second only to the lung cancer here.

14:11

* Kresge 502 Cart: And then, if we look at the age incidence curve, there are a couple of of interesting facts factors here. One is that the age. Incidence incidence curve is quite steep in sort of early pre menopausal years, up to around the time of menopause, when the the rate actually flattens a little bit more after menopause

14:31

* Kresge 502 Cart: and then continues up, and you can see the differences by race and ethnicity here. So what can you see if we look at

14:55

* Kresge 502 Cart: non-hispanic black with the squares here versus non-hispanic white in the circles here. It's a little harder to see down at the bottom. But can somebody describe what they see here.

15:05

* Kresge 502 Cart: I would say that the rise in Hispanic white in the older age is a bit steeper than me.

15:36

* I'm just in that age group of like 60, 60 more, I mean the steep is higher.

15:44

* Kresge 502 Cart: right.

15:53

* Kresge 502 Cart: but in general it appears lower, altogether right, except for at the very bottom here, which again is a little bit hard to see. But it appears that at younger ages black women have a higher incidence of breast cancer

15:55

* Kresge 502 Cart: compared to white women, and in terms of looking at Hispanic of any race you can see, the curve here tends to be lower than both.

16:08

* Kresge 502 Cart: So, thinking about the question in the poll.

16:19

* Kresge 502 Cart: Okay? So then, if we look at trends over time, so on the left is what we call Dcis, so ductal carcinoma in site 2, which is considered stage 0. There is some controversy about whether we should call it carcinoma or not, and then invasive breast cancer. So stage one through 4 on the right, and if we look just at the black

16:26

* Kresge 502 Cart: bar here as anybody over age 20, and then the pink bars split it by younger ages, 20 to 49, and then 50 plus. And you can see some some differences here if we just focus on the invasive breast cancer curves to begin with.

16:52

* Kresge 502 Cart: what are the patterns, and what do you think might be contributing to some of the changes that we see over time?

17:10

* Kresge 502 Cart: So, first of all, what are you seeing

17:19

* Kresge 502 Cart: just descriptively.

17:22

* age 56.

17:30

* Kresge 502 Cart: So you see an increase in the particularly in the 50 and older. Right? Yeah. And then what happens?

17:31

* Okay.

17:40

* yeah.

17:43

* Kresge 502 Cart: And then it decreases.

17:45

* Kresge 502 Cart: Yeah. So and then you see a similar, but perhaps even more sharp increase in the Dcis.

17:48

* Kresge 502 Cart: So what do you think could be contributing to this.

17:57

* Kresge 502 Cart: Not sure. What is that?

18:03

* Kresge 502 Cart: I'm still sharing a screen. That's weird. Okay.

18:09

* Kresge 502 Cart: there we go. No, I'm not still sharing the screen. Okay.

18:14

* Kresge 502 Cart: try again.

18:23

* Kresge 502 Cart: Okay.

18:32

* I'll try not to touch too many buttons. Ok, so what do you think could be contributing to this sharp increase that we saw in the eightys and early ninetys

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* sanctions.

18:47

* Kresge 502 Cart: lifestyle changes

18:48

* Kresge 502 Cart: such as

18:50

* Kresge 502 Cart: Hi, so you can certainly think about whether there are changes in lifestyle changes in the risk factors. And so you could think about smoking's not a huge risk factor for breast cancer rates have gone down in women in the Us. So that's probably not a contributor.

18:59

* Kresge 502 Cart: There is now standard screening and mammography for recommended

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* Kresge 502 Cart: from the age of 50 or 40, but in certain population and high-risk populations, even younger, with other mortalities, screening

19:33

* Kresge 502 Cart: for about 50 years. Right? Right so. And this is a place where patterns of risk factors can change and obesity can contribute to this, but the really sharp increase is most likely due to screening. And in fact, this, this deeper increase in Dcis. These are very small tumors that are not easy to detect by lumps.

19:47

* Kresge 502 Cart: and so, but they are detected by screening mammography. So this is responsible for a lot of that increase in the incidence over time, and then it does tend to flatten out a bit. Anybody have any ideas? Why, we see a decline in about the early 2 thousands.

20:11

* Kresge 502 Cart: Does anybody know anything about the Women's Health Initiative trial?

20:43

* What was that? Yeah. The hormone replacement therapy that was found to be associated with that

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* Kresge 502 Cart: currently vascular races. So because

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* Kresge 502 Cart: practices were changed during that time. That's exactly right. So this, the results of the study was a long term trial of hormone therapy. In postmenopausal women, and as they published their initial findings with an increased risk of cardiovascular disease and an increased risk of breast cancer, thousands and thousands of women stopped taking hormone therapy, and it was in the early 2 thousands. And we can actually see that change in the breast cancer incidence.

21:04

* Kresge 502 Cart: And we'll go through hormone therapy in its relationship with breast cancer. But I think these curves, we tend to think, why is breast cancer increasing over time? But you can actually see increases and decreases related to particular events that were pretty widespread, both screening and this massive drop off in the use of hormone therapy. So it's kind of a fascinating way of looking at these.

21:32

* Kresge 502 Cart: All right. So breast cancer, we say breast cancer. But it's actually a very heterogeneous disease. And I think that this is probably something that you've talked about in relation to other cancers, or you will get to it in other cancers throughout the the course. And initially. One way of looking at this was by using gene expression and categorizing breast tumors by common gene expression patterns.

21:57

* Kresge 502 Cart: And what ended up being defined are these 4 or 5 different subtypes of breast cancer and the different subtypes have very different outcomes in terms of prognosis. So if we look at luminal A and luminal B. Those are the dark blue and light blue curves. So, and this is sort of an initial set, and then a validation set.

22:22

* Kresge 502 Cart: and then basal light, which are also similar to triple negative, which you may have heard about, and the herb, which is her 2 positive tumors, had a much worse prognosis, as you can see here and now, I will say that the her 2 positive tumors.

22:46

* Kresge 502 Cart: the prognosis for those, is actually a lot better now, because we have a targeted treatment for these tumors. So this is something that went from being a prognostic indicator of poor prognosis to becoming an indicator of a tumor that's going to respond to a very effective treatment. But nonetheless, it shows you that these molecular subtypes actually do have meaning in terms of what the natural history of

23:03

* Kresge 502 Cart: the disease and the outcomes could be. So this is established based on gene expression. When we try to classify tumors by their molecular subtypes and epidemiology studies for thousands of tumors. We don't have the resources to do gene expression on all of them, so we can classify them based on expression of a few different markers. So

23:28

* Kresge 502 Cart: estrogen receptor is one of the original classifiers of breast tumors, and whether there are estrogen receptors that are present in the breast tumor.

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* Kresge 502 Cart: Those are er positive versus absent or er negative, and then within those we can use a few other markers to help us define luminal a and luminal B, which are both under the er positive, and they can either be her 2 negative and low grade, or her 2 positive or high grade. So these are all under er positive, and they get split a little bit into luminal A

24:04

* Kresge 502 Cart: in limital b, and then under the er negative, we have the her 2 enriched. So these, her 2 positive tumors, which I just mentioned, have this very effective targeted therapy, or the basal like, which are negative, for all of these markers, as well as being positive for 2 additional ck, 5, 6, and Bgfr

24:29

* Kresge 502 Cart: and then there's sort of this unclassified where they're negative for all 5 of these markers. And one of my colleagues at 1 point had said, I think they're just. They're they're positive for something. We just don't know what to look for yet in terms of subseting these tumors.

24:51

* Kresge 502 Cart: so when we think we can then lump them a little more. So, there are hormone receptor, positive tumors that are H negative or H 2 positive, and then her 2 overexpressing tumors. And then these triple negative tumors. So they're er negative Pr negative and her 2 negative. And I have the gray and pink dots here to help line up with what we're going to look at in the next side. So on the left side, this is looking at breast cancer, incidence and death.

25:09

* Kresge 502 Cart: By race and ethnicity. So if we're going to look at a white, black and Hispanic as the as I had in the poll. Question. First of all, what do you see for incidence rates in the light pink bars

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* Kresge 502 Cart: across these categories.

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* Kresge 502 Cart: Why?

26:03

* Kresge 502 Cart: right? So higher incidents than the white women

26:07

* Kresge 502 Cart: black women are just a little bit lower. And hispanic women are lower than that, and then in dark pink are the mortality rates. So what what do you see here? So if we look at black versus white.

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* Kresge 502 Cart: In terms of mortality. What do we see?

26:30

* Kresge 502 Cart: Right? So the mortality rates are higher in black women. Right? Yup. So that helps answer our question. And then, if we look at the on the right side, so this shows the distribution within these categories of race and ethnicity, the distribution of these molecular subtypes of breast cancer. And so if we again compare white versus black here, so the dark pink are the hormone receptors, tumors.

26:38

* Kresge 502 Cart: The light pink are the her 2 and hormone receptor positives. So those are sort of like the luminal, a luminal B, and then the light gray are the her 2 enriched tumors, and then the Darpa Gray are the triple negatives. And so, if you compare these distributions between white and black women, what do we see

27:05

* Kresge 502 Cart: but someone from this side of the room. What do we see?

27:42

* Kresge 502 Cart: Alright portion of the

27:50

* Kresge 502 Cart: I'm sorry I really got vision, and I'm trying to read it. Hr. Negative for 2 negative

27:55

* right? So black women have a higher proportion of their breast. Tumors are these triple negative tumors.

28:01

* Kresge 502 Cart: and they have a worse prognosis. So triple-negative tumors. We don't have a very good target therapy for so the hormone receptor doesn't express an estrogen receptor. Negative

28:07

* Kresge 502 Cart: tumors are harder to treat, and they're more aggressive. So they have a worse prognosis. So some of this difference in mortality between black and white women could be contributed by the difference in the distribution of subtypes

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* Kresge 502 Cart: and the other thing that that contributes to the difference in these subtypes is, if you think about the age incidence curve that we're looking at in younger women black women have higher incidence rates than white women, but then, in older women it reverses, and the

28:48

* Kresge 502 Cart: proportion of tumors that are triple negative tend to be higher in younger women. And so a lot of these patterns are going together, contributing to the difference in mortality rates. Now there are lots of potential differences in structural access to care, treatment, screening

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* Kresge 502 Cart: all of these things can also be contributing to some of the disparities that we're observing between the mortality in white women and black women. But there are also some molecular differences that are adding to that as well

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* Kresge 502 Cart: any questions on this.

29:46

* Kresge 502 Cart: All right. So when we come back to the question, most of you picked the one that shows that although white women have the highest incidence rates for breast cancer, black women have the highest mortality rates, so it is racial disparities, but it shows up in a nuanced way in terms of the incidence and mortality

29:53

* Kresge 502 Cart: that's good when you adjust for the subtype.

30:16

* Kresge 502 Cart: Yes, that's a great question, and yes, you can account for some of that difference by the molecular subtypes. But, as I was saying about structural differences in structural racism. There are differences in mortality that remain that are likely to do things that are not related to the molecular characteristics of the tumor.

30:20

* Kresge 502 Cart: Other questions.

30:47

* Kresge 502 Cart: alright, yes. it's good to see you nice to see you too.

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* Kresge 502 Cart: first. But I was just wondering why black it's more than twice

31:01

* Kresge 502 Cart: right. It's a great question, and I don't think we have the whole answer for it. One of the reasons is that they tend to have more breast cancers at younger ages, and those tumors that develop are are slightly more likely to be triple negative tumors. Some of it could be related to the fact that we'll get into some of the reproductive factors. But after pregnancy, the the risk of breast cancer

31:12

* Kresge 502 Cart: increases for a window of 5 to 7 to 10 years after a pregnancy, and those tumors are slightly more likely to be triple negative tumors. So, seeing that, you know, increase the higher incidence rate in black women in younger ages they're gonna be more likely to be triple negatives which could be contributing to this.

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* Kresge 502 Cart: There may be other differences contributing it as well. But it's a good question.

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* Kresge 502 Cart: Other questions.

32:01

* Kresge 502 Cart: Alright.

32:06

* Kresge 502 Cart: so when we look at breast cancer survival, we've talked a little bit about it already. But one thing to note overall. What do you see from these?

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* Kresge 502 Cart: So this is looking at five-year survival in the left hand, ten-year and fifteen-year survival. So just looking at the five-year survival.

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* Kresge 502 Cart: you've probably talked about some other cancers in the class. What? What stands out to you about breast cancer?

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* Kresge 502 Cart: What's that relative to 2 other cancers? There's higher.

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* Kresge 502 Cart: Yeah, yeah, so 5 years survival, 90% sounds pretty good. Right? It is pretty good. And it is different, you know. Compare that to something like pancreatic cancer, where you'd actually almost see the reverse of that. What do you see when you look at 5 year 10 year 15 year overall still pretty good. But what do you see?

32:37

* Kresge 502 Cart: Sorry

33:00

* Kresge 502 Cart: it decreases, it decreases. So with the tenure and the 15 year. And this is something that is a little more unique to breast cancer. So with colon cancer for women and men who survive 5 years, you're pretty much in the clear if you make it to 5 years.

33:01

* Kresge 502 Cart: have a good odds of much longer survival with breast cancer, there tend to be later recurrences, causing death, 10 to 15 to 20 years after the initial diagnosis of breast cancer

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* Kresge 502 Cart: more unique to breast cancer. And it's a big question of why does this happen. And in fact, we talked a little bit about the fact that triple negative tumors have a worse prognosis. They're more aggressive. But there are a lot of er positives. So there's hormone receptor, positive tumors that can recur 10 to 15 to 20 years after that initial breast cancer diagnosis

33:37

* Kresge 502 Cart: and then ultimately cause breast cancer death. So that's something that is certainly a remaining question. To try to understand. Why is it that these tumors recur much later? And what can we do about it? How can we try to prevent some of those occurrences so

34:02

* Kresge 502 Cart: overall great survival rates, but still a lot to be figured out and potential places to intervene. If we can figure out how to do that.

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* Kresge 502 Cart: is that

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* Kresge 502 Cart: disease related deaths, or like, this is breast cancer, specific death? Yeah. Yeah. Good question. Right so. And and given that the overall breast cancer survival is very good. Most women who are diagnosed with breast cancer end up dying of another cause. But there is a significant breast cancer, death. As you go out.

34:29

* Kresge 502 Cart: So if we look at the survival rates by race.

34:55

* Kresge 502 Cart: you can see how it changed over time. So if we look overall at all races, you can see 5 year survival rates started at 75% in the up to 91% in the. And if we look at white versus black, you can see increases in both. However, at each time period they're lower for black women than for white women.

35:00

* Kresge 502 Cart: and I just wanted to show one other bit here in thinking about the disparities. So so this shows overall what we've looked at already. So this is 5 year survival rates for white women is 92% and 83% in black women. And we've looked already at the difference in molecular subtypes. And here you can look at the differences by

35:28

* Kresge 502 Cart: whether the tumor is localized or has spread regionally or more distantly. And you see these disparities at each stage. This does not account for molecular subtypes, but I think if you adjust for those molecular subtypes, you still see that there's a disparity in the survival between black women and white women.

35:52

* Kresge 502 Cart: Any questions?

36:16

* Kresge 502 Cart: All right. So that gets us through some of the descriptive epidemiology. Now we'll turn to getting into a little more detail in the risk factors. So I want to just give you an overview of the risk factors that are pretty well established at this point. So age we looked at the age, instance, for if you could see that it goes up, that's clearly a strong risk factor. Gender. We know that women

36:21

* Kresge 502 Cart: are much, much more likely to get breast cancer. Men do get breast cancer, but it is predominantly showing up in women. family history and genetics.

36:45

* Kresge 502 Cart: So some of you had put up Brca. One lb. 2 ATM. These are inherited mutations that carry a very high risk of breast cancer over lifetime. There are also genes that are more common snps that contribute a little bit to increasing risk of breast cancer. And you can think about. I don't know if you've talked about polygenic risk scores, but some of these more common mutations that

36:55

* Kresge 502 Cart: are associated with a slight increased risk can add up, so that if women have multiple markers they can end up with higher risk of breast cancer, benign breast disease is something that is now more commonly detected, thanks to mammography. And these are lesions that are not malignant. But they aren't changed.

37:20

* Kresge 502 Cart: They're from normal tissues. So they have hyperplasia, abnormal growth. That isn't cancer, but it increases a woman's risk of developing breast cancer. Later we'll get into endogenous hormones. So thinking about estrogens and androids that are naturally circulating in the body. Breastfeeding is associated with lower risk radiation. So when you have radiation to the chest increases, risk.

37:44

* Kresge 502 Cart: mammographic density which you can detect on a mammogram will go through exogenous hormones. We've already talked about hormone therapy, and we'll get into a little more detail alcohol, adipocy and physical activity. And so, as I noted. One of the pieces that you'll see here is that there are risk factors that occur across the life course. So we'll start with some of the earlier risk factors and think about

38:12

* Kresge 502 Cart: how they could be impacting risk of breast cancer decades later, and what that might mean.

38:37

* Kresge 502 Cart: So one of the things is thinking about windows of susceptibility. So when we think about changes in development over the life course, there are specific windows when there are really big physiologic changes that occur in the mammary gland. So you think about going through gestation, puberty, and then pregnancy and lactation. And so at each of these developmental stages there are chances that

38:44

* Kresge 502 Cart: risk factors could be having an impact on the development of the breast tissue on how breast tissue changes after pregnancy and lactation. Things like that. So this is sort of a conceptual model that was put together from a working group looking at environmental factors and their impact on breast cancer. But it's a good conceptual framework to think about the major phases

39:13

* Kresge 502 Cart: of life course development that parallel the development of carcinogenesis.

39:38

* Kresge 502 Cart: So as we go from prenatal early childhood, puberty, pregnancy, pre-menopause, postmenopause. You can think about changes in the breast tissue that could be happening along these same lines. So normal breast tissue progressing to hyperplasia, etc. And then the rainbow is representing the fact that etiologic factors could come into play at multiple levels of thinking

39:43

* Kresge 502 Cart: of the biology as well as behavioral and social levels that could be playing a role in these different windows of susceptibility.

40:08

* Kresge 502 Cart: So one of the really interesting pieces of evidence that suggests that

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* Kresge 502 Cart: childhood and puberty are a particular window of susceptibility, for breast cancer is actually looking at breast cancer rates in women who were exposed in Japan to the atomic bomb.

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* Kresge 502 Cart: And if you look at this, this is the age at which the the women were at the time of the bombing. So this is a very unique point in time exposure. And then looking across the life course after that, to understand the impact of that radiation exposure on the risk of breast cancer. And so you can see the relative excess risk. And so can somebody describe what you see here

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* Kresge 502 Cart: incidents. if exposed to the

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* Kresge 502 Cart: on if exposed, and I think your age is higher compared to people who are exposed to.

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* Kresge 502 Cart: or laughter

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* Kresge 502 Cart: right? So it turns out that women who were exposed in their thirtys, fortys and fiftys had not much of an elevation of risk of breast cancer compared to the women who were exposed when they were children, or in their teens or twentys. So this really highlights for us that something really important is going on in the breast issue at that time, when the radiation exposure occurred in those younger ages.

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* Kresge 502 Cart: You think about the radiation causing mutations that can then be carried on. They're impacting much more in the younger women in the younger breast tissue

42:00

* Kresge 502 Cart: sort of background evidence for us to think about. Okay? Well, what other exposures might be occurring in childhood and around puberty that could be impacting risk of breast cancer throughout the woman's life.

42:14

* Kresge 502 Cart: So one of the things that we're so let's see, several of you had put into the word cloud adaposity or childhood obesity. And so, looking at childhood weight is something that shows up as being a breast cancer risk factor, but potentially not in the direction you were thinking. So. The way we've gotten at this in several studies is by asking, women

42:27

* Kresge 502 Cart: call their body size or their body shape when they were different ages in childhood. So we use a pictogram like this, and ask the women to tell us what their body shape was like at age 5 and age 10, and we can use an average of that childhood, and then at age 20, and we can think about an average of 10 and 20 as being what they were like

42:52

* adolescents.

43:17

* Kresge 502 Cart: So this may seem like a fairly crude assessment of this, but it actually tracks pretty well with weight and bmi that were measured at age 18, where we can look at old records and compare that to the recalled body shape. And so it actually validates quite well. And what we see is the following. So if we look, this is looking at

43:18

* Kresge 502 Cart: average body size between ages 5 and 10. So thinking about this is childhood. And then this is the average scores from that pictogram. And this is in premenopausal women and in postmenopausal women. And so you can tell me what they see here.

43:45

* Kresge 502 Cart: Is this the direction you would have expected?

44:11

* Kresge 502 Cart: No.

44:16

* Kresge 502 Cart: let me see this.

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* Kresge 502 Cart: the higher the it's not defined by these integrals. The higher the

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* Kresge 502 Cart: rescue way that

44:34

* Kresge 502 Cart: the smaller the rate of breast cancer. And in premier puzzle women. It starts from the beginning, starts after the first to measurements or system.

44:38

* Kresge 502 Cart: So to me this is really striking, not only the inverse association, but the fact that it's something that lasts for many, many decades. So what a woman's body size was in in adolescence is impacting risk of breast cancer in her. In postmenopausal women. So really coming back to that windows of susceptibility. There's something going on at that moment that is potentially a set point. It's establishing something in the breast tissue that then gets carried on

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* Kresge 502 Cart: throughout life. And it's really pretty striking, also a very hard message to think about with public health. This is not the message that we're thinking is the right thing to pass along.

45:29

* Kresge 502 Cart: So we also see it with both risk of er positive and er negative tumors. And so as we get a little further into thinking about adulthood adiposity. We'll see more of a difference between er positive and er negative but in this case childhood adiposity seems to be associated with lower risk of of both types of tumors.

45:41

* Kresge 502 Cart: So this was done in the nurses, health studies, but it has since been replicated in many other studies than many other populations. So, looking at a Japanese population, African, American, Scandinavian, all show this lower risk of breast cancer with higher weight at adolescence, child or adolescents. So it's really quite consistent

46:03

* Kresge 502 Cart: over many, many studies

46:26

* Kresge 502 Cart: question ready for biological explanation. Yeah, great question. I think later, I will show those same pictograms

46:31

* Kresge 502 Cart: with mammographic density. So we do see that it's associated with mammographic density. And so again, I think there's something about establishing. It's changing the breast tissue at that very early age and having some impact. But I think we're still missing a lot of those molecular pieces to really understand what's going on.

46:41

* Kresge 502 Cart: Yes, on the previous slide.

47:03

* Kresge 502 Cart: Oh, yeah. So this is taking the average of these numbers. Sorry, it's a good question. So we averaged between ages 5 and 10, and you'll note that you know, our highest category here is is 5 and a half plus. So it's really sort of lumping all of these larger sizes into that higher category. Yeah. Well, but no, it's a great question. It's not very well labeled here. So thank you.

47:10

* Kresge 502 Cart: great. Okay. So

47:35

* Kresge 502 Cart: then, age at monarchy is a pretty well established risk factor for breast cancer, and this shows decreasing risk with every year later that monarchy occurs. So this is when a woman starts having her menstrual cycle, and essentially the breast tissue is undergoing changes in development at that point.

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* Kresge 502 Cart: And so here you see the longer monarchy, that initiation of Menzies is delayed, the lower the risk of breast cancer. Now, what do you make of the? If you look at

48:03

* Kresge 502 Cart: at this slide

48:16

* Kresge 502 Cart: versus this slide.

48:18

* Kresge 502 Cart: Did these? Did this make sense?

48:21

* Kresge 502 Cart: Does anybody know anything about adapting and monarchy, and how those go together?

48:25

* Kresge 502 Cart: Okay.

48:39

* Kresge 502 Cart: so do you know, if overweight, girls are more likely to have an earlier period or a later period when they first start.

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* What's that earlier?

48:55

* Kresge 502 Cart: Right? So these 2 go a little bit at odds. They're not going in the same direction. And yet both of these are pretty strong. And.

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* Kresge 502 Cart: you know, independent risk factors. So it is sort of fascinating to think about what's going on and trying to to disentangle this and we can see, you know, this is sort of thinking about this life course, exposure to estrogen. So the earlier monarchy starts the earlier you start on this you know, big curve of being exposed to estrogen estradial over the life course.

49:07

* Kresge 502 Cart: and then comes back down in menopause with menopause. So thinking about age, at monarchy. So one thing that has changed, you can see the Bmi in young adulthood is associated with. So this is the odds of having an earlier monarchy so higher. Bmi is associated with higher odds of having an early monarchy. So, just as you said.

49:31

* Kresge 502 Cart: overweight is usually associated with an earlier monarchy, and we can see that in this it's a big collaborative study that pulled together here in Japan

49:55

* Kresge 502 Cart: something like 40 50 studies. Oh, 117. I was way off. The other thing that's interesting is looking here. And what do you see in terms of year at birth.

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* Kresge 502 Cart: with odds of having an earlier monarchy?

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* Kresge 502 Cart: Exactly.

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* Kresge 502 Cart: it increased

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* Kresge 502 Cart: so at higher odds of earlier monarchy with later ages, later births, later birth, years. So later, birth cohorts. So over time, age at monarchy has been getting earlier and earlier. And so there are lots of factors that go into this. But if you look back at historical records, I mean, it's gone from an average age of 1716 to, you know, down

50:28

* Kresge 502 Cart: 1211, and getting younger all the time.

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* Kresge 502 Cart: So we can then think about how things like this could impact risk of breast cancer over time. So these are things that are changing. This is a much slower change than perhaps the obesity epidemic, but it is nonetheless contributing to potential changes in breast cancer incidents

51:00

* Kresge 502 Cart: that we can look at as diet and lifestyle in childhood and try to understand whether those have an impact on agent monarchy and in the growing up today study, which is the children of the nurses, health study to participants. We've looked at a variety of different dietary factors, and I think Walter Willett was really assuming that it was going to be related to milk consumption, but found no relationship between milk, consumption, and adolescence

51:20

* Kresge 502 Cart: and onset of of monarchy, however, sugar sweetened beverages, so drinking lots of soda was associated with earlier onset of monarchy, so there are some shifts in our diet and lifestyle habits that are contributing to some of those shifts in monarchy as well, and probably lots of other aspects of the way our lives have changed, too.

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* Kresge 502 Cart: Any questions on this.

52:15

* Kresge 502 Cart: Was there a biological explanation, for

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* Kresge 502 Cart: we see childhood associated with?

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* Kresge 502 Cart: It's a good question, and you can think about the sort of pro insulinemic and very pro growth factor, aspect of adipoity and obesity could be contributing to some of those changes associated with earlier monarchy. There are probably other avenues and pathways that that are could be explored in terms of trying to understand that. But it is. It's an interesting one.

52:26

* Kresge 502 Cart: So this reduces the risk of breast cancer. It doesn't increase the risk of eating

52:58

* Kresge 502 Cart: grants and system

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* Kresge 502 Cart: childhood adiposity. No agent! Oh, agent monarchy! So that's a good question. And I don't know that it's been picked up as a risk factor for other cancers.

53:05

* Kresge 502 Cart: I don't believe that it's related to ovarian cancer, at least not strongly.

53:19

* Kresge 502 Cart: Alright, so we'll keep going with reproductive factors and starting with pregnancy and age at first birth. So here this is from some breast cancer risk modeling that some of our colleagues have have done, and it shows 3 different incidents. Curves for hypothetical women who in the black line a woman who didn't have any children

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* Kresge 502 Cart: in the red line. A woman who had one child starting at age 35, and in the green line a woman who had 4 children starting at age 20. And so what do you see here?

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* Kresge 502 Cart: What would you say in terms of pregnancy and age at first birth, and how they impact breast cancer risk.

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* Kresge 502 Cart: Yes, right? So, having a earlier age at first birth and and pregnancy becomes protective, then so you have a lower risk of breast cancer compared to women who don't have any births. And then, if you have a a child late in life, then that we call sort of the bump of increased risk after pregnancy

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* never quite comes back down. So those women have a higher risk of breast cancer compared to women who didn't have children, or compared to women who had children at an earlier age.

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* Kresge 502 Cart: pregnancies or just. I mean.

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* Kresge 502 Cart: maybe, that those who had pregnancy at the younger age also had pregnancies. Right? Yes, you're right, you're right, and that's a good point. So tends to be women who have more pregnancies have a lower risk of breast cancer.

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* Kresge 502 Cart: But if the woman who had her first birth at age 35, and then had 2 more children, she still would be at an elevated risk of breast cancer compared to another person. It's a great point, though. Good question.

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* Kresge 502 Cart: all right. So we talked about those windows of susceptibility and what's going on in the breast tissue, and the breast tissue undergoes tremendous change with pregnancy and birth and lactation. And so you can think about a later age at first birth has more time between monarchy and the time of the birth, so that breast tissue develops.

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* Kresge 502 Cart: and then it undergoes these huge changes, and there's more chance for mutations to be accumulated in breast tissue, and then pregnancy throws all these hormones at the breast tissue, and can contribute to replicating some of those mutations that have been accumulated, whereas women who have a childbirth much earlier, that window between monarchy and childbirth is shorter, and fewer mutations would have had the chance to accumulate at that point

56:08

* Kresge 502 Cart: happens with the breast tissue physiologically, and then after birth and after lactation, the breast tissue undergoes pollution, and you end up with more differentiated cells in the breast tissue compared to women who haven't had children, and that actually helps protect against development of breast cancer.

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* Kresge 502 Cart: I did mention, though, that there is this window after a pregnancy where the risk of breast cancer increases. And so here you can see this is a large pooled analysis across many cohort studies where you can see the risk associated with

57:00

* Kresge 502 Cart: the risk of breast cancer associated by time since most recent birth. So here you can see this spike, and it does take a while to come back down.

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* Kresge 502 Cart: Typically, we think about this window of susceptibility after a pregnancy as being sort of between 5 and 10 years. And again, think about those accumulated mutations having had this big flesh of hormones. That's a point that those mutations could be replicated and turned into a cancer at that point.

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* Kresge 502 Cart: So the pregnancy and birth is sort of a tricky one in terms of thinking about the impact on breast cancer risk. So breastfeeding or lactation has shown pretty consistent evidence across many studies that breastfeeding is associated with a lower risk of breast cancer. And it does seem to be dose dependent.

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* Kresge 502 Cart: independent of parity. So if a woman breastfeeds has one child in breastfeeds for a very long time that accumulates that that benefit of lesbian. And recently there's been evidence that that suggests that this benefit is particularly notable in triple negative breast cancer. So Tnbc's triple negative breast cancer. And again, those are more likely to be diagnosed after pregnancy. So, having this benefit of breastfeeding

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* Kresge 502 Cart: on the breast tumors, particularly the triple negatives, it's a nice thing to be able to see.

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* Kresge 502 Cart: So this is showing the lifetime duration of breastfeeding and risk of breast cancer. And again, this is from one of these large collaborative studies pooling the original data. It's not a meta analysis. It's actually pooling all of the original data and showing the lower risk of breast cancer with longer duration of breastfeeding. And this is accounting for the number of births that a woman had, too.

58:52

* Kresge 502 Cart: Questions on this.

59:17

* Kresge 502 Cart: All right. So age at menopause.

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* Kresge 502 Cart: Again. If you think about the Orange graph that I showed about that exposure to Estradiol and the earlier you go through Menarche, the earlier you start that large exposure to circulating estrogens, and on the other end of the spectrum age at Menopause.

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* Kresge 502 Cart: The later an age at menopause is, the more it stretches out that exposure to high levels of Estradiol. So a later age at menopause is associated with a higher risk of breast cancer. And you can see this particularly contrasting a woman who has a bilateral efrectomy. So both of her ovaries removed before the age of 45, has about half of the risk of a woman who goes through menopause

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* Kresge 502 Cart: after age 55. So it really does have quite a big impact in terms of thinking about ultimately the risk of breast cancer, and we can see it even looking at ages of natural menopause between age 50 and 55, as you can see here in the figure.

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* Kresge 502 Cart: questions on this

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* Kresge 502 Cart: alright.

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* Kresge 502 Cart: So thinking about the circulating hormones, we've done quite a bit of work trying to understand how. Oh, yes, go ahead

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* Kresge 502 Cart: for the check

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* Kresge 502 Cart: age at monarchy is associated with higher increases of breast cancer leader in life and early generations.

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* Kresge 502 Cart: But you see that early days

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* Kresge 502 Cart: so early monarchy is not associated with early menopause. It's just a question of you can have variation in both spectrum. So puberty at age 11 or age 15, for natural menopause, it's usually between 45, and 55. But it's usually independent of monarchy. So it's not a fixed amount of time

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* that the woman has.

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* Kresge 502 Cart: So if you think about again thinking about the exposures of estrogen. If you extend that on either end, because of earlier monarchy, or because of later menopause, you end up with an increased risk of breast cancer. But actually, if you think about it, the longer you have that reproductive span.

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* Kresge 502 Cart: whether it's by earlier menarchy and or major menopause that are highly risky breast cancer.

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* Kresge 502 Cart: Yes.

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* Kresge 502 Cart: I just had a few questions regarding women that can't have children. What is the difference in risk for that population. Good, really good question. And there's been a lot of interest in this

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* for women who have infertility and does the infertility impact breast cancer risk. And if women have infertility treatment, does that impact breast cancer risk? And there's been a lot of studies on this. And actually, nothing is showing up as being either terribly consistent or terribly strong in terms of it being a risk factor for breast cancer. But it does get you to wonder like biologically.

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* Kresge 502 Cart: Is there a hormonal link to the infertility. Could that be driving it in one way or the other? I think you can think about

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* Kresge 502 Cart: some women may, if you have polycystic, ovarian, ovarian, syndr, poly, cystic, ovary, syndrome. You tend to have higher androgen levels which are associated with higher risk of breast cancer, but it's not that consistent that we see, you know, infertility being associated with a higher or a lower risk of breast cancer?

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* Kresge 502 Cart: Good question.

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* Kresge 502 Cart: And of course there are lots of different treatments for infertility, many of them hormonally related. So there's a lot of interest in it, but not a lot of evidence

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* Kresge 502 Cart: in a reassuring way, I should say there have been lots of studies, but nothing is showing it very consistently. Yes.

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* Kresge 502 Cart: and they have this. I understand that we can see this video related to Lower Lisbon breast cancer by apply the H. 2.

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* Kresge 502 Cart: The people who get after 35 is annually

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* Kresge 502 Cart: breast cancer, you know to be. have any space. Do you have any experiences?

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* Kresge 502 Cart: Right? Right? So it is sort of thinking about this that you commonly think that women who have children have a lower risk of breast cancer than women who haven't had children. Pregnancy makes a difference because of what has been probably accumulated in breast issue up to age 35. That then gets replicated.

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* Kresge 502 Cart: Sort of terminal differentiation of the breast tissue happens so much later, after a late pregnancy that you end up with as actually being at a higher risk than Malibu.

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* Kresge 502 Cart: so many nuances in breast cancer. Yes, I'm not sure if there's data on this. But has there been a study looking at age of birth and 35 of the skin patients in it. The risk model here actually takes into account the spacing of the birth.

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* Kresge 502 Cart: And so there is some impact there that a woman who had a birth at 20 to 23 has a lower risk than a woman who had a birth at 20 and 35, but that 20 to 35 is still not as high as this

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* 35 year old, because she'd been through the pregnancy early at age 20.

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* Kresge 502 Cart: That make sense. Yeah, the good question.

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* Kresge 502 Cart: Bernie Rosner, who's a Biostatistician here, has done a lot of this modeling, and he came up with what he calls the birth index, which is a way of accounting for the age of pregnancies, the number and the spacing between the births. He has that all into one variable in the model, because the spacing does have an impact.

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* Kresge 502 Cart: Other questions

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* Kresge 502 Cart: alright. Okay. So we'll move on to endogenous hormones. So thinking about the hormones that are naturally circulating in our bodies, and there are a couple of ways that these can contribute to development of cancer. One is through proliferation. So hormones are acting as growth factors, and this increases opportunity for replicating a mutation that already exists in the tissue. So more cells

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* Kresge 502 Cart: at risk of mutation occurring as well as promoting the growth of cells that have a mutation. After that initiation. There's also the possibility that estrogens could be contributing to cancer through genotoxic mechanisms. So estrogens get metabolized through hydroxylation.

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* Kresge 502 Cart: Yeah.

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* Kresge 502 Cart: so they can actually create atoms in the DNA and contribute to damaging the DNA and hypothesized to be genotoxic.

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* Kresge 502 Cart: So, thinking about again another way of thinking about cycling hormones. So we looked at the overall curve between before monarchy and then reproductive years, having a very high level of Estradiol. And then after menopause, and this looks at the monthly cycle and the variation in hormones, and you can see in the light blue bars. This is showing the mitotic rate of breast

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* Kresge 502 Cart: cells, and you can see that it changes over the month of the period cycle, the menstrual cycle. So when estrogens and progesterones are high in the ludal phase, you can see that the mitotic rate, the rate of division of these cells in the breast. Epithelium is higher at that point. So this was a good hypothesis that these hormones are contributing to

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* Kresge 502 Cart: proliferation.

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* Kresge 502 Cart: So we've done a a number of studies. It's hard to look at Plasma Estradiol in pre-menopausal women. For exactly this reason, looking at the blue bar, depending on what day of the cycle. You measure it. You're gonna get very different estrogen item

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* Kresge 502 Cart: levels. So what we were able to do in the nurse's health study, too, is, ask women to collect samples that were timed in the menstrual cycle, so we asked them to collect them in the early follicular phase, when estrogens are pretty low, as well as in the mid-ludal phase, when estrogens are pretty high, and what we found was an increased risk with higher levels in the follicular phase. So in that sort of low end of the estrogen spectrum.

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* Kresge 502 Cart: and as we pooled our studies together with other studies of pre-monopausal circulating hormones. pretty,

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* Kresge 502 Cart: I would say, suggestive. It's still not really robust, but pooling together did show an increased risk of breast cancer with higher circulating levels of Estradiol. And this is looking at a range of normal in women. So women who tend to be on the higher range of normal for circulating estrogens have a higher risk of breast cancer.

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* Kresge 502 Cart: And then, in looking at Android, so circulating testosterone Andrine Dione, it is also fairly consistent across studies that higher levels in premenopausal women are associated with a higher risk of breast cancer.

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* Kresge 502 Cart: So we know in premenopausal women, most of the estrogen is produced in the ovaries which can then impact the breast tissue, as we can see in that mitotic rate. So after menopause.

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* Kresge 502 Cart: the ovaries no longer produce estrogens, but they keep producing androgens. So post monopausal women are still producing androgens, both from the ovaries and from the adrenal glands. And what happens is those androgens actually get converted into estrogens in the adipose tissue. So there are enzymes in the adipost tissue that can convert androgens into bioactive estradiol.

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* Kresge 502 Cart: So in postmenopausal women, those circulating estrogen levels which are much lower than they were in premenopausal women are are related to how much adipose tissue there is.

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* Kresge 502 Cart: So if you look at circulating estradiol levels among women across different Bmis, so different adiposity. You can see higher estrada levels in the overweight and obese women and lower estradiol levels in the Lemur women. So

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* Kresge 502 Cart: you can think about the

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* Kresge 502 Cart: thinking about adiposity. We know that adiposity is contributing to circulating estrogens. So if we measure those hormones in postmenopausal women. And again, this is measuring a normal range of Estradiol. But women who are in the top

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* Kresge 502 Cart: 20 to 40% of those circulating levels are at a higher risk of breast cancer. So this is looking at a couple of different estrogen. So estridiol and estroan, sulphate as well as testosterone. So circulating androgen levels are also associated associated with higher risk in postmenopausal women.

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* Kresge 502 Cart: and one of the things I had looked at was whether the circulating hormone levels were still predictive of risk. If somebody had a higher risk of breast cancer based on their pregnancy, history, and their family history, and their history of benign breast disease. And we see that it's similarly predictive of higher risk, independent of some of these other risk factors.

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* Kresge 502 Cart: So any questions on the circulating hormones.

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* Kresge 502 Cart: So as we talked about, we'll get into a little bit of some of the modifiable factors. But you can think about how these relationships with the circulating hormones may be related to some of the factors that we're going to talk about. So we'll start with weight. And so here again from grand bullets. And Bernie Rosner, thinking about this, the modeling of risk between lean in the green dashed line, average weight in the red and then obese in the blue.

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* Kresge 502 Cart: Tell me what you see here.

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* Kresge 502 Cart: Yes, just to understand. Oh.

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* Kresge 502 Cart: one is that the graph? Just question whether the lean average weight in obese was it defined? At what age was it at younger age, or at the time of diagnosis across the life course.

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* Kresge 502 Cart: Average weight orderly. That's a good question. And you're just going to say it has a much higher incidence of obese persons as they learn

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* Kresge 502 Cart: right. But what happens early? What do you see early

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* Kresge 502 Cart: in the last 2?

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* Kresge 502 Cart: But it's, in fact, on the low end that occurs. So just as we talked about childhood adipocy contributing to a lower risk of breast cancer. Here you can see that adiposity throughout the reproductive years is associated with a lower risk of breast cancer, too.

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* Kresge 502 Cart: Excuse me, swallowed my water round.

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* Kresge 502 Cart: and then these lean women, who we know, if you're lean as a child, you're at an increased risk of breast cancer. But after you reach menopause, you end up benefiting from being lean. Right? So we can think about. As a woman enters menopause. The adipose tissue that she's carrying is contributing to those circulating hormones. So you end up seeing a higher risk of breast cancer in the obese woman and the lean women end up, then switching to having a lower risk of breast cancer.

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* Kresge 502 Cart: But this is one of these. This is one of those hard to think about in terms of public health messaging. It's great to be overweight in terms of breast cancer risk before menopause. But then it's bad after menopause, and also, by the way, it's not great for other chronic diseases. So

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* Kresge 502 Cart: it's a hard one to think about. But this is very, very consistent. So I wanted to show you. This is a more recent pooled analysis that pulls together many, many studies, including our health study and nurses. Health study, too.

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* Kresge 502 Cart: So this is looking at Bmi between 35, and 44. So we already looked at childhood. And now we're looking sort of the middle of those reproductive years. And you can see this very consistent dose response relationship between increasing Bmi at these ages and lower risk of breast cancer. And

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* Kresge 502 Cart: you know, some of this could be well were they overweight as a child, and maybe they got the benefit then. But even when we adjust for childhood out of posterity, we still see this relationship, that it's an inverse association with breast cancer risk.

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* Kresge 502 Cart: But then it changes again as we saw in that first curve, it changes with menopause. So looking at

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* Kresge 502 Cart: overweight after menopause. So this is looking at weight change since age 18. And Bmi, we know, is not the greatest measure it gets at out of posterity. But if you think about weight change since age 18 in most people, and weight that is gained is adipose is adiposity sort of across the life force. So we can see here that women who gain weight have a have a higher risk of breast cancer

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* Kresge 502 Cart: after menopause. And this is among non-hormone therapy users, because again, we know that adiposity contributes to circulating estrogen levels.

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* Kresge 502 Cart: And if you add in hormone therapy, you're already adding lots of exogenous hormones which is going to increase your risk. So you can most clearly see the association between adiposity and breast cancer in women who are not taking hormone therapy, and we see this coming back to the er status of the tumor, we see an increased risk with weight gain for the er positive tumors that are fueled by estrogens.

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* Kresge 502 Cart: and we don't see much of an association at all with er negative tumors that are not fueled by estrogens. So this suggests to us that adiposity is contributing to risk likely through a hormonal pathway.

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* Kresge 502 Cart: So one of the things that I was interested in was was, well, if women can lose weight, does that lower their risk of breast cancer? And, as you can imagine, it's very hard to study women who have lost weight and chucked it off. For a long time. We had to wait a long time in the nurse's cell study to be able to do this analysis. But we see that women who lose weight after menopause

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* Kresge 502 Cart: are at a lower risk of breast cancer, and in the dark blue bars there are people who lost the weight and were able to keep it off. And interestingly, in a lot of studies. We've seen this again in a large pooled analysis as well, and it doesn't seem to matter why women lost weight, so you can think about was the weight, loss, intentional or non intentional.

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* Kresge 502 Cart: But, in fact, your adipose tissue and those circulating estradiol levels. It doesn't matter whether it's intentional or not intentional. It is contributing to lower estrogen levels overall

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* Kresge 502 Cart: any questions on that on out of custody.

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* Kresge 502 Cart: All right. So hormone therapy. I'm going to remind you about the incidence curves over time, and how we saw that decline in the curve after the publication of the Women's Health Initiative. So in our studies we see and had seen long before the Women's Health Initiative was published an increased risk of breast cancer with use of men, pausal, hormone therapy, and it increases with longer duration.

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* Kresge 502 Cart: Use so estrogen plus progestin for less than 5 years, and then this is estrogen plus proges. For more than 5 years

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* Kresge 502 Cart: now we do see in our cohorts an increased risk with estrogen alone, whereas women's health initiative, actually saw an inverse association. There are a lot of differences between the randomized trial and observational studies, one of which is the women in Women's Health initiatives started taking hormones

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* Kresge 502 Cart: many years after the onset of menopause, which is not typically how women take them now, or had taken them previously, so that could have contributed could be chance one way or the other. But it is a difference between the randomized trials and the observational study. But the plus P. So the estrogen plus proges is very consistent.

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* Kresge 502 Cart: And then you can see here this is again this large pool of analysis, looking at estrogen plus progestin, and going up to a 2 and a half fold increased risk for women who've taken it for more than 15 years of use.

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* Kresge 502 Cart: and then past users. So once women go off hormones, as we saw in that decline in the incidence of breast cancer over time, they have a lower risk of breast cancer compared to women who are current users.

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* Kresge 502 Cart: So you can think about it as you go off hormone therapy, and it sort of puts the brakes on whatever in terms of growth, being fueled by those hormones.

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* Kresge 502 Cart: So, and then thinking, putting together the hormone therapy and the adiposity. This is sort of a nice figure looking at the incidence of breast cancer. Among this is across Bmi, so different categories of Bmi and looking at estrogen and progestin use so exogenous hormone therapy, estrogen only. So this sees a a difference, but still an increased risk.

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* Kresge 502 Cart: The way we had seen in estrogen only, and then this is among never users looking at the across Bmi, so you can see an increased risk of breast cancer with higher Bmi. And then this splits it out by whether it was er positive tumors or er negative tumors, and you don't see much difference

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* Kresge 502 Cart: for er negative tumors. But you do for er positive. So I like this because it sort of puts into the same figure what the impact is of endogenous circulating hormones from higher Bmi versus adding, exogenous hormone therapy and looking at the impact on breast cancer?

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* Kresge 502 Cart: All right. Questions there.

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* Kresge 502 Cart: Yes. just the

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* Kresge 502 Cart: to the presence of prisons. Vary on. If it's brca, one or 20, great question. It does so. Brca, one tumors, I think, are more likely to be brca, one vary.

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* Kresge 502 Cart: Yes. Yeah. Good question. Yeah.

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* Kresge 502 Cart: Alright, so we'd already seen the impact. I just wanted to show you this is looking at the seer data from California, where you can see again this big drop off in breast cancer incidence.

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* Kresge 502 Cart: right after the self initiative was published, and all these women stopped taking hormones. So I always think it's epidemiologically kind of neat that you can see the impact of a pretty wide population level change in a risk factor.

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* Kresge 502 Cart: Okay? So again, showing you the exposure to Estradiol over the lifetime weight adds after menopause, and then thinking about hormone therapy, and how much that adds. So just thinking biologically, what's going on with hormones.

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* Kresge 502 Cart: alright oral contraceptives are associated with an increased risk of breast cancer. But oral contraceptives tend to be taken by younger women who are at lower, absolute risk of breast cancer. And so and then, after people stop using the risk declines so that there's 10 years after stopping oral contraceptives, there's no increased risk

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* Kresge 502 Cart: of breast cancer.

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* Kresge 502 Cart: Okay, so I'm gonna try to go through some of these next few slides a little quickly. So we I can spend some time on the mammographic density. So alcohol is a very consistent modest but consistent risk factor for breast cancer. And you can see it, even at pretty modest drinking levels, that there's a significant increased risk of breast cancer. And it seems to be for both er and er negative tumors.

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* Kresge 502 Cart: Carotenoids are the colorful fruits and vegetables that are high in Alpha Keratin and Beta Carotene we can see a lower risk of breast cancer among women who have higher circulating levels of carotoid. So we can measure this in the blood about a 15 to 20% reduction in breast cancer risk

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* Kresge 502 Cart: for women in the top. Fifth, compared to the bottom. Fifth. And here we see the opposite of atop. We actually see a stronger association between carotenoids and er negative breast cancer. So it seems like they are more beneficial for preventing these more aggressive, harder to treat tumors. So this is a highlight. I like that. We could all stand to eat more fruits and vegetables, and it could benefit breast cancer, risk as well.

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* Kresge 502 Cart: Physical activity, modest but pretty consistent, associated with a lower risk of breast cancer more convincing

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* Kresge 502 Cart: were consistent among postmenopausal. But it does seem to impact both, and Iarch did conclude that there was convincing evidence that it reduced risk of breast cancer, and we can see it in our cohorts. And one of the things again that I'm interested in is there a message we can say it's never too late to modify your behaviors that could impact, risk. And so we looked at whether women who change physical activity after menopause

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* Kresge 502 Cart: could change or had a lower risk of breast cancer. And we did see women who were not very physically active before menopause, but became physically active after menopause had a lower risk of breast cancer compared to women who were consistently low physical activity.

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* Kresge 502 Cart: So here's sort of a summary of thinking about the impact of modifiable factors. So the mean incidence rate in the population is here. When we look at single factors, if we set population levels to the lower risk for weight change. So adiposity, menopausal, hormone, therapy, alcohol, physical activity and breastfeeding. We can see the impact that this would have on incidence. And

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* Kresge 502 Cart: and when we put it all together. It has a pretty substantial impact on the incidence of breast cancer. So nice again to think about, are there ways we can modify lifestyle diet things like hormone therapy that can reduce the risk of breast cancer.

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* Kresge 502 Cart: Okay? So mammographic density well established, positive association between mammographic density and breast cancer risks. And this shows there's legislation now that requires women to be informed whether they have dense breasts on a mammogram.

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* Kresge 502 Cart: So this shows you going from a gradient of very fatty breast tissue to very dense breast tissue, and how it shows up on a mammogram, and underneath it shows the relative risk associated with these categories. So it's pretty striking a fivefold increased risk for women who are in the top quartile of density compared to women in the bottom, having no breast density.

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* Kresge 502 Cart: And so one question is, well, what you know what's going on here, and one aspect of it is, you know, could it be that

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* Kresge 502 Cart: dense breasts are much harder to find a tumor in compared to fatty breast tissue, and if you look at the time from mammogram to diagnosis, you see that there is a higher relative risk in that earlier time period, but that then, you know, the risk continues so you could think about. You know many of the cases that are diagnosed

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* Kresge 502 Cart: within a year or 2 after a mammogram. It could be that the breast density is a masking the tumor, and that it's hard to detect. But the fact that 10 years later women who, with dense breasts have a higher risk of breast cancer suggests that the breast density is showing us something about risk. It's not just

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* Kresge 502 Cart: masking an existing tumor is the use of ultrasound and MRI chained.

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* Kresge 502 Cart: I mean, this is from 95. Yet. Now we use multiplied for these.

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* Yes.

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* Kresge 502 Cart: right? So that's a good question. So maybe this is actually lower, because we're detecting them better if they get moved on to the next step. And that's a great question. I actually don't know that it's possible. But my guess is that there's still some that are gonna be hard to detect.

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* Kresge 502 Cart: So this is with er status. We see a mammographic density associated with both er negative and er positive. And remember, I was. Gonna I mentioned this that we see again these measures of adiposity in childhood. With the average over age 5 to 10, so that the women who were more overweight as children

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* Kresge 502 Cart: have lower mammographic density much later in life. So clearly, I mean that to me points to something happening at the level of the breast tissue early on in life. That's kind of a set point creating a difference in that breast tissue, and we can see that the

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* Kresge 502 Cart: association between childhood adiposity and breast cancer risk is mediated somewhat by mammographic density. So it's like between 30 and 50% whether it's Premenopausal or postmenopausal women. So some of that relationship between adiposity and breast cancer risk, we're picking up through a mammographic density relationship.

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* Kresge 502 Cart: any questions on that.

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* Kresge 502 Cart: So I will say one other thing that's pretty cool about mammograms today is

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* Kresge 502 Cart: clinically, they're categorized in density. But you can imagine that maybe with AI there could be lots more information in this image. And so we've been working with some colleagues at Mit and at Mass general who are using AI tools to develop or to get more information out of the mammogram beyond

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* Kresge 502 Cart: demographic density. So, reading the pixels at a much finer level and finding that there is more information about breast cancer risk. Biologically, we're not understanding it yet. But I think there's more to be gleaned there.

1:29:02

* Kresge 502 Cart: Okay, so I have one final menti, and that is, can you name a breast cancer risk factor that was new to you today?

1:29:16

* Kresge 502 Cart: And I'll switch over to the final question here.

1:29:25

* Kresge 502 Cart: Are there anything that you had not heard about

1:29:31

* Kresge 502 Cart: adipasty. It's an interesting one, isn't it? Not so straightforward in breast cancer.

1:29:43

* agent, monarchy, great.

1:29:51

* Kresge 502 Cart: Another audacity. Lower Bmi. In early life. Yeah.

1:29:55

* Kresge 502 Cart: Monarchy.

1:30:02

* Kresge 502 Cart: obesity

1:30:05

* Kresge 502 Cart: great. So it sounds to me like, maybe you had heard about some of the reproductive factors being associated with breast cancer, risk, and hormone therapy, perhaps but thinking about what's going on early in life is is new for a lot of you, and it's pretty fascinating, and I wish we had better answers to try to tease it apart. But I'll leave that. I'm happy to say. If people have questions and thanks for your attention and your contributions.

9

* Perfect. So Hi, everybody nice to see you all. It's been a little while since we've had our cancer epi trivia. So we thought, we'll start with that. Then we're going to turn it over to Colleen Michelle, who are going to give a presentation about survival in cancer, both methodologic as well, some substantive work. And then, after that.

1:16

* Kresge 502 Cart: we're gonna discuss the article that was by welcoming day. We'll actually have you turn to your neighbors and have a little group discussion. First, we're gonna pose a few things for you to think about while you're talking about the paper, and then we'll all come together, and I know there's been some great comments already on the Harvard Canvas board which we're really looking forward to see, and then also kind of have that discussion.

1:38

* So why don't we turn first? And so I guess. Can you see the

2:03

* Kresge 502 Cart: where do you? How will they see that? Sorry?

2:10

* Kresge 502 Cart: Oh, my goodness, why don't.

2:18

* Kresge 502 Cart: did I? Okay.

2:20

* Kresge 502 Cart: maybe that's so strange.

2:24

* Kresge 502 Cart: Oh, maybe I'm just saying the meeting's pretty important. This is our sharing.

2:40

* Kresge 502 Cart: Oh, starts video.

2:48

* Kresge 502 Cart: yeah.

2:51

* Kresge 502 Cart: Desktop.

2:59

* Kresge 502 Cart: Do you know how to do it on a PC

3:13

* prostate cancer survival.

3:36

* So the question is among prostate cancer patients, what is the primary cause of mortality after a diagnosis of prostate cancer. Is it a prostate cancer?

4:01

* Kresge 502 Cart: Is it B. Death from other cancers? See Alzheimer's disease

4:12

* Kresge 502 Cart: and or d cardiovascular disease? And so now I can't see in. But then we can show the responses.

4:18

* Kresge 502 Cart: Ok. Got it so they can see each other. Got it. Ok? So 2 people who logged in

4:30

* Kresge 502 Cart: 6 people

4:39

* Kresge 502 Cart: 7.

4:43

* Kresge 502 Cart: So let's give it 15 more seconds.

4:47

* Kresge 502 Cart: 10 more seconds.

4:55

* So

5:01

* 5,

5:03

* Kresge 502 Cart: 4, 3, 2, and one. And then where is it? Sorry?

5:06

* Okay.

5:14

* Kresge 502 Cart: sit on the screen.

5:16

* Kresge 502 Cart: Oh, wow! All right. So 6% of people said, prostate cancer.

5:18

* Kresge 502 Cart: 18% said death from other cancers. 12%, said Alzheimer's. But in fact, the main cause of death is cardiovascular disease. And if you looked at currently today, all prostate cancer patients, about 30% of deaths, cohort is cardiovascular disease. But actually, death from other cancers is actually quite high as well. And then Alzheimer's disease

5:28

* Kresge 502 Cart: disease is kind of about the same as prostate cancer mortality is, it's different, depending on the stage of diagnosis. So if you have an asthmatic prostate cancer diagnosis, about 90% of deaths argue with the cancer itself

5:53

* Kresge 502 Cart: set

6:12

* Kresge 502 Cart: before we get started. Just a reminder. You are hosting an office hour related to the letter to the editor this afternoon, right after class. If you have any questions that is due on Thursday at midnight.

6:22

* Kresge 502 Cart: you are welcome to work on your own or up through groups of 3. If you don't need to tell us in advance. You can just submit it as a group of 2 or 3. Just make sure everyone's name is on it very clearly

6:38

* Kresge 502 Cart: any questions on that. If it's a collaborative letter.

6:53

* Kresge 502 Cart: yeah. And what person was submitted, we only need one copy as long as everyone's name is on it, and the total length of the one that a single person could do, or if you were to submit a real letter to the editor, it could be a solo effort. So we wanted to mimic that as close as possible

7:05

* course

7:30

* Kresge 502 Cart: any other questions.

7:31

* Kresge 502 Cart: and then we will hopefully turn back your descriptive of the individual assignments between tomorrow or before class on Thursday, and then you should have gotten your presentation assignments as well.

7:34

* Kresge 502 Cart: The text of the letter yeah. The header could be separate. Yeah.

7:53

* Kresge 502 Cart: Sorry, guys, it looked really weird.

7:57

* Kresge 502 Cart: And I did it from my laptop.

8:01

* Kresge 502 Cart: Okay?

8:05

* Kresge 502 Cart: Oh, it just didn't let me share. You couldn't see the slides. Well, yeah.

8:07

* Kresge 502 Cart: sorry. Someone created a separate desktop on this. And so we don't know how to close it on here. Thanks for bearing with us.

8:29

* Kresge 502 Cart: Okay.

8:39

* Kresge 502 Cart: And then are you sure your screen? Yes.

8:40

* Kresge 502 Cart: I don't think so. Yep, just like share on some.

8:46

* It's

8:57

* Kresge 502 Cart: quite so. Nope.

9:00

* I'll be

9:03

* Kresge 502 Cart: okay.

9:25

* No cause you can still see.

9:26

* Sorry guys.

9:33

* Kresge 502 Cart: please select the very specific.

9:37

* Kresge 502 Cart: Oh, I was selecting only the slides, but since it's plugged into my entire. Oh, okay.

9:39

* Kresge 502 Cart: I'll try it again.

9:54

* Kresge 502 Cart: So much.

9:56

* Kresge 502 Cart: That's interesting.

10:03

* Kresge 502 Cart: You'll switch to the screen.

10:22

* Okay? Yeah.

10:27

* Kresge 502 Cart: Oh.

10:29

* Kresge 502 Cart: thank you for your pat issues.

14:20

* Kresge 502 Cart: Hello. And. Mary.

14:40

* Kresge 502 Cart: we can use the team.

14:44

* Alright, we're gonna start talking about some considerations for studies in cancer survival and cancer survivorship and a brief overview of what we'll be talking about. So we'll provide an overview of the burden of burden of cancer survivorship in the Us.

14:46

* Discuss a proposed research framework for working with studies of cancer survivorship, discuss some potential biases and measures that you'll see in these types of studies. Michelle will talk about some next steps in this research space, and then we'll give you a very brief overview of our research, which is in this space.

15:09

* Kresge 502 Cart: So I'll start with an overview of cancer survivorship. Just so, you know, in our work. And in this presentation we'll be using the definition of a cancer survivor that is used by the American Cancer Society as well as other institutions like the Nci, which is that someone is considered a cancer survivor at the point at which they're diagnosed meaning they are a cancer survivor from the day. They're diagnosed onwards through their treatment and potential eventual remission.

15:27

* Kresge 502 Cart: So areas of concern in this research space is very wide in scope, but might include things such as the effects of certain treatments, comorbidities, as well as effects on homoridities that are incident because of treatments such as cardiotoxic effects, like laurel, said about cardiovascular disease and prostate cancer survivors

15:54

* Kresge 502 Cart: as well as disease, progression, quality of life, metrics concerned with the well being of cancer survivors, both physical psychosocial as well as specific symptom burden. And then, of course, mortality, which is what we see in our survival studies.

16:14

* Kresge 502 Cart: So just to put a figure to what we're talking about the current estimates are that there are over 18 million individuals in the Us. Who are considered cancer survivors and comparing that to our total Us. Population that makes up over 5% of the total population. It's projected that this group will increase as well with an estimate of over 22 million by the year 2,032 and 26 million by the year 2,040.

16:31

* Kresge 502 Cart: So this figure just puts it on the same statistics that I just outlined, but breaks it down by age group. And of course we can see that the older age groups are where we see the greatest proportion of individuals who are considered cancer survivors. But I'll just highlight here on the very bottom. This is our group of individuals who are younger than the age of 50, and you can see that there has been an upward trend in this group contributing a larger proportion of cancer survivors, and that's projected to increase through 2040 as well.

17:01

* Kresge 502 Cart: So as noted, the number of cancer survivors is expected to grow. This can be attributed to a number of different things, including screening and diagnosis and potential over diagnosis as well as treatment advances.

17:32

* meaning that we're able to treat and manage the disease a little bit better in individuals. And hopefully, this makes sense of the figure tending to increase. If we go back to our Fb. 201 basics of what a prevalence is, it's a function of incidence which we have from increasing hypnosis as well as duration, which comes from both diagnosis where we're hopefully able to diagnose individuals at earlier stages as well as treatment advances where

17:46

* hopefully able to extend the survivorship period within reasonable burden.

18:10

* Kresge 502 Cart: So when we're talking about survival of cancer patients. Typically, you'll see statistics of the 5 year survival. That's kind of the standard metric that you'll see in population based studies

18:16

* Kresge 502 Cart: and across all cancer sites. It's estimated that the five-year survival is around 69, and that goes down when we're talking about more extended survival periods upwards of 18 for 20 year survival hopefully, that makes sense, though, since, as we talked about, most individuals are older age over 2 thirds of cancer survivors are over the age of 65 in the Us.

18:28

* Kresge 502 Cart: It's really important to consider that these statistics that we have are across all cancer sites and the site specific statistics are really important to look at individually as we looked at last week. There are certain cancer sites where the majority of diagnoses are in stages, 3 or 4 where individuals have advanced disease, and therefore the prognosis is a little bit shorter and more grim. And so, looking at site, specific statistics is really important.

18:52

* Kresge 502 Cart: This is just a graph that I included in case there was some interest of consideration of the differences, and how different cancer sites and demographic characteristics are contributing to the prevalence of survivors.

19:23

* Kresge 502 Cart: And so, as alluded to all of the cancer sites, we're contributing to some of these statistics. There are specific cancer sites where we have the much more cancer survivors who are living longer because these are sites that have greater treatment options and have screening programs that allow individuals to live longer beyond their diagnosis. So the majority of cancer survivors in the Us. Are breast cancer, prostate melanoma and polar rectal cancers.

19:38

* Kresge 502 Cart: But you can see this in perspective to some of the other major cancer sites of what groups are really contributing to that figure of 18 million individuals.

20:07

* Kresge 502 Cart: Stage is another really important factor to consider individuals who are diagnosed in their earlier stages might have better treatment options potentially curative treatment options. If cancer is diagnosed in Stage one and it's confined to this specific organ of interest, and the tumor is able to be removed from surgical procedures. There might be greater options for extending survival

20:20

* as opposed to someone who essentially has stage 3 or 4 disease. And we need systemic options that are trying to target each and every cancer cell in the body. But this represents a really important group of individuals who have advanced disease and specifically metastatic disease, who have potentially unique needs and contribute a large portion to the cancer survivorship population. In the Us. The current estimates are just over 600,000 individuals are metastatic cancer survivors specifically, and this figure itself has also projected to increase.

20:43

* Kresge 502 Cart: This is hard to see the difference in colors on here, but this is a breakdown of that group of individuals broken down by whether or not, they had de novo metastatic disease, or presented with metastatic disease or diagnosis versus recurrent metastatic disease.

21:17

* Kresge 502 Cart: And with that, then I'll transition over all right. So now we're going to talk about cancer survivorship research framework.

21:34

* Kresge 502 Cart: so in collaboration between Bergmann Woman's Hospital, Harvard Medical School and Ci experts, policymakers, advocacy groups and cancer survivors. The cancer survivorship care quality framework was created. And this framework is an interplay of individual interpersonal organizational community and policy factors. Of course. But today we'll be focusing on the

21:43

* individual level factors. So this framework serves as a foundation to define 5 domains of cancer survivorship care as well as general needs for this patient population. So the domains are interrelated and codependent on each other, of course. But consideration of these domains can help us think about research questions and developing ideas that we want to do research on improving the quality of life.

22:09

* improving care, access to care and overall outcomes for cancer survivors.

22:33

* Kresge 502 Cart: So let's get started. So the first one is reoccurrences and new cancers. So cancer survivors are at an increased risk for reoccurrence of primary cancer. But also the development of new cancers as well due to their genetic predisposition. So hence there's a need for surveillance for subsequent cancers, such as through repeated physical laboratory tests

22:40

* Kresge 502 Cart: and imaging. So if you recall from a couple of weeks ago, when Dr. Eliison came and spoke about breast cancer, hormone, receptive, positive breast cancer is the most diagnosed subtype of breast cancer that we see.

23:04

* Kresge 502 Cart: and for hormone receptor, positive breast cancer endocrin therapies used as a adjuvant treatment to reduce the risk of reoccurrence, and that's also to reduce the risk of death.

23:18

* Kresge 502 Cart: However, for a lot of populations, especially vulnerable populations, such as individuals of color, individuals who may not have insurance or speak different languages. Adherence can be so optimal, so assessment of adherence, of adjuvant or risk reducing strategies can help identify populations who are at higher risk and who may need additional interventions as well.

23:29

* Kresge 502 Cart: Next, we have physical effects. So cancer survivors are at risk for physical effects of cancer as well as treatment. Of course, this depends on what type of cancer individual diagnosed with and the type of treatment that they're treatment plan that they're going through. So this requires assessment of symptoms, conditions via medical history and physical examination. So, of course, there are various treatments and different combinations of treatments.

23:57

* Kresge 502 Cart: But some of the side effects that can come with this, for example, with chemotherapy, include nausea, fatigue, constipation, diarrhea, hair loss, chemo induced neuropathy. Amongst many others.

24:26

* Kresge 502 Cart: Next, we have psychological or psychosocial effects. Sorry so similarly to physical effects, psychosocial effects, the type and extent of surveillance will depend on the cancer type and treatment. Of course. So this can be done via assessment of symptoms and conditions using validated questionnaires and instruments.

24:43

* Kresge 502 Cart: So some examples of psychological effects include anxiety, depression, cognitive changes, fear of reoccurrence, and then, on the other side, some social effects include financial toxicity, loss of work, productivity, return to school change in insurance status, interpersonal issues, such as with family and caregiver relationships as well.

25:05

* Kresge 502 Cart: Next, we have health promotion. So just because someone has a cancer diagnosis, this does not mean that. And an individual will change their health behaviors at the drop of a hat.

25:32

* Kresge 502 Cart: So, in fact, a lot of research research shows that cancer survivors tend to be more obese, less active, and have higher levels of smoking than those who do not have cancer. So assessment of live self behaviors is needed when we're talking about cancer, survivorship care. And this can range from asking questions about physical activity, smoking, cessation, age and sex for chronic conditions and vaccinations as well.

25:44

* Kresge 502 Cart: And lastly, we have chronic conditions. So so far, we've noted that physical effects and psychosocial effects after treatment are some of the domains that we want to focus on. But it's also important to acknowledge that there are some high prevalences of front conditions both before and after diagnosis of cancer and some non-related non cancer-related conditions include hypertension diabetes, cardiovascular disease. Copd, amongst many others

26:13

* Kresge 502 Cart: this week. Yeah, go ahead. Last point I would just mention, because

26:46

* Kresge 502 Cart: chronic diseases. Today, we know that all these exposure to chemotherapy causes changes in the deep, and we call them today.

26:53

* Kresge 502 Cart: And there are changes in it that occur with age which is interesting to the last couple of years. We now know that

27:01

* Kresge 502 Cart: the modification of all these work, or a lot of these modifications and chronic conditions, go through all these modifications in the DNA. So there's actual pathogenesis of the DNA changes that makes cardiovascular toxicity higher calculation. And there are papers on copd immunological diseases.

27:12

* Kresge 502 Cart: So we know another piece of that, not just association, but also the part of physiology.

27:34

* Thanks.

27:44

* So care for cancer survivors is complex. And in the Us. We have a very complex health system. So aspects of getting care for cancer survivors includes primary care, oncology, survivorship, clinics, the type and availability of providers offering care overall access to care, communication and decision making cancer treatment plans across health teams.

27:48

* access to research participation and patient caregiver experiences within just the health care system itself. And of course this can differ based off of how individuals may identify. So across race gender identity, socioeconomic status just to name a couple.

28:15

* And of course, then, comes into question, how do we measure this in the spatial population? So, of course, some of these outcome measures are not necessarily distinct for the spatial population. But these measures can help researchers identify gaps in care and survivorship experiences.

28:35

* So outcomes include health related quality of life, including physical, mental, emotional, social functioning, healthcare utilizations, specifically like emergency care, hospitalizations, critical care, use.

28:52

* Kresge 502 Cart: cost of care, including those to the patient health care, system and mortality. So all cause mortality and cancer specific mortality. So an example for health-related quality of life measures that we use.

29:05

* Kresge 502 Cart: Me and colleen are the er Tcg. 30, which is a validated questionnaire for health, related quality of life among cancer survivors, and is applicable in over 100 languages, which is a functional assessment of cancer therapy questionnaire. And that questionnaire also has extensions for specific cancer sites as well.

29:22

* Kresge 502 Cart: Ok, great. So transitioning to specific considerations for epidemiologic studies of cancer survival. Specifically.

29:53

* Kresge 502 Cart: we wanted to just flag a few measures that you'll see. Commonly some of these will be very familiar, hopefully, and just a caveat that we're talking in the probability framework here, but of course, these can be extended to event analyses, and so measures. You'll see, as Michelle alluded to include all cause mortality, where we're looking at the total number of deaths across the population as well as cause specific mortality. We're concerned with death due to a specific cause, say cardiovascular disease.

30:04

* Kresge 502 Cart: And then there are some other measures that might be of interest. For example, overall survival within the cancer population where we're looking at the number of patients that are alive after some period of time. Like, I said, a lot of the time we'll see metrics of this five-year period among the total cancer patients for that site. There's also relative survival, which is a comparison of the overall survival for a specific cancer

30:33

* site and a comparison of that overall survival among a similar but cancer-free population to try to deduce the effect of the cancer on survival.

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* Kresge 502 Cart: And then also, we, of course, have cause specific survival which is related to that specific mortality measure. Again, an interest of not dying of a specific cause. Among the total population of patients

31:07

* Kresge 502 Cart: there are a number of potential biases that we think about often when we're designing studies of cancer survival. These are not unique to cancer, epemiology, or even chronic disease equity. But we do see them in this space fairly often, and this is not any means to try to tell you how to fix a study. If you have these issues, there's whole chapters on some of these or whole classes on some of these issues

31:22

* Kresge 502 Cart: here. So this is just a brief overview, so that you're familiar, the first of which is competing risks. So to define a competing event is something that inhibits our ability to observe the event of interest.

31:47

* So, for example, in our studies of cost, specific survival, say, breast cancer, specific survival or breast cancer specific mortality on the flip side. If someone died of cardiovascular disease that would be a competing event that precludes our ability to have seen them die of breast cancer. To handle this, there are a number of different modeling frameworks and decision to make as someone who's designing this study.

32:00

* including using a cause, specific hazards approach or a sub distribution hazards approach. You can learn about that in Biosat 223. There is probably a month's worth of lecture on that.

32:24

* Kresge 502 Cart: Another issue that you might see is immortal time. Bias so immortal time can be defined as a period of time where it's not possible for study participants to have the event of interest, such as a death, for example. And that's why it's quote unquote, immortal.

32:36

* Kresge 502 Cart: I'm just going to hopefully see great that work. There are a bunch of different ways that a mortal time bias can come up in our studies and function as a specific type of bias. But it's really a nature of the determination of an individual's treatment status or their exposure status involves some delay in between the time that they're enrolled and your time of starting follow-up and their actual treatment received

32:53

* Kresge 502 Cart: depiction. There's this exposed group on the top, and an unexposed group on the bottom follow up, started, but we did not observe anyone have their first prescription, which made them exposed of this study of, say, a prescription drug use

33:20

* Kresge 502 Cart: until this time point, but because we observed that we know that they didn't die any time before that, however, they weren't exposed at that time. So it's kind of misclassified person. Time there again. This is a really complex issue, and if you want to learn more about it. You can take bias at B 203, where you'll have a great Tf. Next semester. We'll talk about this Michelle

33:34

* Kresge 502 Cart: and if you want to learn more about mobile time by his colleague is linked this paper that goes way more in depth, with different types of moral sign bias

33:58

* Kresge 502 Cart: and describes different types that can occur and what to do in your study design to prevent it, maybe. Can you talk just very quickly? If you were designing the study differently, or could you to get rid of the immortal times? Example?

34:09

* Kresge 502 Cart: Yeah. So the kind of way to make sure that you don't have a mortal time bias. One of the ideal ways is to emulate a target trial which a lot of the folks in the causal inference space here talk about B 289. If you're in lab right now, and F 207 will talk about that extensively. But the ideal way to do that is that you choose a time scale at which you can align the time 0 where you start, follow up the eligibility of being in the study, and then the exposure determination, so that you don't run into this issue of potentially

34:25

* Kresge 502 Cart: and having misclassified for some time is one option. Yes, alternatively. You could also take that period of time where your treated individual is not being exposed at that point in time, and just consider them unexposed for that period of time as well.

34:56

* Kresge 502 Cart: All right. So the next bias that we would raise is lead time bias, lead time bias as well as length. Bias are particularly relevant in studies of cancer screening, which is what we're going to talk about a lot more today.

35:17

* So the lead time is the time between which a cancer is detected by screening versus the time between which it would have been detected by symptomatic presentation and going to the doctor and diagnosed.

35:29

* And so I have a graphic here that shows that as well. I believe the paper where this is from, as well as a very technical source. If you want to get into the math behind this, which I don't want to. But you can see here, if we attribute that the null hypothesis is true that screening truly doesn't have an effect on prolonging someone's survival. The patient would have died at the same period of time.

35:43

* Kresge 502 Cart: Whether they were screened or not, you can see that being diagnosed by screening in this upper group. Here they appear to be surviving longer than the group that was diagnosed, based off of their symptomatic presentation. So it looks like screening is effective for survival

36:07

* Kresge 502 Cart: moving on to length bias. So length bias is another concern in these studies of cancer screening or other screening across disease areas. Probability of being in your sample is proportional to some characteristic. And in the case of cancer screening.

36:27

* Kresge 502 Cart: If that works great. It might be related to the screen detectable period in which we are able to observe that tumor, and if more indolent tumors have a longer screen detectable period than, say, an aggressive tumor where they have symptoms starting sooner, we are more likely to observe individuals that have this longer period of potentially being detected by screening. And again, this can overestimate the effectiveness of screening

36:53

* Kresge 502 Cart: great. And the last issue we wanted to raise was on prevalent users. So this is a bias that occurs. If you are looking at a study where you're not looking at an incident exposure meaning something that is starting new, but rather something that individuals could have been doing beforehand, say, taking some drug versus not taking some drug as your comparison, but they have been taking it

37:24

* all along before they were even thought to be in your study. So this is an issue that arises where, if the exposure was truly harmful and you include these prevalent users. Anyone that would have been harmed by that might not be in your population, there might have been a depletion of susceptible individuals, in which case the people in your study might not be representative of the true effect of that exposure and outcome relationship.

37:47

* Kresge 502 Cart: This is just a kind of overview of all of this again, not meant to be comprehensive, but just to provide you with some things to think about. If you're designing these studies.

38:12

* Kresge 502 Cart: Okay?

38:23

* So now we want to talk about some next steps in cancer, survivorship, survivorship research.

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* Kresge 502 Cart: So we can use research to improve clinical care, quality of life and understanding of adverse effects of treatment to improve the health and well-being cancer survivors and caregivers.

38:33

* Kresge 502 Cart: So we can do this by defining population needs for various cancer sites and systematically evaluating evidence gaps when it can inform where needs are not being met. So another thing that we can see is standardizing outcome measures. So, as I mentioned previously. For health related quality of life. There are a ton of different ways that we can measure a health related quality of life for cancer survivors, including the Ertc. In fact.

38:46

* Kresge 502 Cart: but having a standardized method that is commonly used, can allow us to compare more studies that are looking at the same outcome being measured. We can also use methods from implementation, science to disseminate and implement interventions with shown benefit, but also de-implement interventions that have shown no benefit or have been seen to be harmful for cancer survivors as well.

39:12

* Kresge 502 Cart: So we just wanted to share some funding research opportunities that are currently available for research work into cancer survivors, including an Ro one. We're looking at research to understand and address survivorship needs of individuals living with advanced cancer. Uon, looking to address the primary care needs of cancer survivors, and another Uon

39:37

* looking at a multi-level approach to conducting underrepresented populations in clinical trials.

40:01

* Kresge 502 Cart: So the Nci office of cancer survivorship actually posted this on their twitter yesterday. And we wanted to share this graphic where it shows the number of cancer survivorship brands that have been funded by the Nci. As of 27 since 2,017. So, as you can see, that number is increasing, and hopefully continues to increase in their patriotism.

40:09

* Kresge 502 Cart: So we can also think about power research methods that we develop can also be used in the clinical setting to improve care for cancer patients. So we can think about how and when clinicians can actively measure quality of life metrics, for example.

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* Kresge 502 Cart: quality of life metrics for their patients while also ensuring that we're not overburdening patients, providers, and medical systems when trying to measure these outcomes.

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* Kresge 502 Cart: For example, this could mean implementing patient navigators who may ask questions while patients are at their visits. Also, we can look at optimization of tools and collecting patient outcomes and processing measures to prevent provider burden, designing effective evidence-based clinical survivorship care providers, practices and health care systems

41:07

* Kresge 502 Cart: to systematically understand patient needs. And lastly, we can think about how we can implement full cancer survivor care quality framework in the clinical setting. So this might be easier to do in a comprehensive cancer center and a lot more difficult to do for smaller, independent oncology, clinics, and consideration of what's more feasible in those settings is also necessary as well.

41:32

* Kresge 502 Cart: And then, lastly, we can think about next steps in policy. So

41:58

* Kresge 502 Cart: our research and what we do in this betting also impacts the policies that are implemented in the United States. So professional guidelines, training, reimbursement and health coverage for post-treatment. Care is definitely necessary and needed. And the research we conduct

42:03

* Kresge 502 Cart: can impact the community level to the Federal level, not to mention policies that impact insurance, professional organizations that promote cancer care and further support advocacy groups as well.

42:21

* Kresge 502 Cart: Umhm. And then we do have 2 slides on our research. But maybe in the interest of time. We'll leave that up. You can come to chat with us if you're interested in what we're working on. We're always happy to talk about it. We both asked our Pq. 2 very recently, so we're happy to chat about it whenever.

42:36

* Kresge 502 Cart: thanks.

42:52

* Kresge 502 Cart: I wonder if you could. Just I think that examples of lead time bias in particular, and as well as the other biases, are interesting as we talk about paper. I wonder if you might have an example of a cancer kind of talking about how long a link bias can be

42:57

* Kresge 502 Cart: like in screening. For example. like prostate cancer. Maybe. Yeah, I mean, prostate cancer would be a good example, potentially of length. Bias where we have these slower, growing, indirect tumors that probably would not have caused severe harm in patients or caused them to die of that. And so it's possible that we're kind of observing more of these individuals that eventually would have been fine as well.

43:13

* do you have an idea for lead time? I have a nice example.

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* Kresge 502 Cart: Think of like metastatic disease, like someone who's

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* Kresge 502 Cart: like there's no potential

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* Kresge 502 Cart: like next steps like in a very extreme case. So maybe they decided to get strained for some reason, before symptoms appeared. But the disease had already progressed, and then comparison to someone who just waited for symptoms to come. But both individuals died at the same time anyway.

43:54

* Kresge 502 Cart: and prostate is interesting from a lead time. Perspective. Is it like moved the diagnosis 7 years earlier to 10 years. So if you think about

44:16

* Kresge 502 Cart: 5 years survival or even 10 years survival for prostate cancer, people will say, Oh, it's 99%. Nobody died. But actually, it's the second reading. So it's interesting how big of an effect. And then, as you mentioned all these other cancers, that all of the burden that comes from

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* Kresge 502 Cart: over diagnosis, too, of anxiety and then unnecessary potential

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* Kresge 502 Cart: treatment. So you might hear sometimes people talk about with I can't feel like we talked about thyroid cancer, prostate cancer, even some breast cancers, maybe, where right here a term called pseudo disease, or actually 2 cancers physiologically. But cancers, people think, would never have progressed, never have caused harm.

44:57

* Kresge 502 Cart: Hi, so so I put a slide deck, and so I think the thought was that we'll give people like little time to just discuss we'll come up

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* discussion. So to put together

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* Kresge 502 Cart: a few slides. So I think, you know, hopefully, everybody's had a chance to read

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* Kresge 502 Cart: article. And just while we're pulling it up I can, just for things we'll be thinking about. So first, I kind of talk about why did Welch and Day even write this article? What was their motivation? Significance was, look at the figures and think about what's your interpretation of their findings? Do you agree with them? Disagree? And why are there anything

45:49

* Kresge 502 Cart: the cancers you've studied colorectal cancer? We haven't talked about prostate cancer yet. But are there things that you wouldn't know about? Cancers that make you think they might have missed the mark a little bit?

46:15

* Kresge 502 Cart: Yeah. And then I think I had a question about Oh, yeah, do you think the the I'm so assumptions that made were reasonable? Why or more, why not so? But really talk about whatever you wanna talk about anything that really resonated with you anything that gave you a little bit of pause and talk with your your neighbor, and then we'll we'll come together, maybe at 30'clock for for discussion.

46:30

* Kresge 502 Cart: Okay, perfect.

46:53

* Kresge 502 Cart: Put some questions there.

58:57

* Kresge 502 Cart: And I know some of you already sent some some good comments on the chat. So okay, let's start. So does anybody want to? Just let's.

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* Kresge 502 Cart: it's always easy to begin, like what was the stated significance of the article.

59:38

* Kresge 502 Cart: Yes, the owners are supposed to attack screening costs so much economic work on their government, and so they want to question that their screening gets helpful. In the first place.

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* Kresge 502 Cart: Ok, that's a good point. So there is economic burden. Any other burdens or other reasons. Yet

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* Kresge 502 Cart: I think that the concept of are we actually saving life? Or are we going to do it? Done at the same time with other conditions, anyways.

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* Kresge 502 Cart: And in that case, isn't it competing on all the other life? Is it just really good causes?

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* Kresge 502 Cart: Right? So yeah, so there's economics. And then how many lives actually save, I guess.

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* Kresge 502 Cart: Okay, any other thoughts?

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* Kresge 502 Cart: Oh, I can see something big. Oh, I'm sorry. I was Ok, a little bit later in the origin. But is it actually hurting people to be undergoing this process?

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* Kresge 502 Cart: Right? So right? So some people may get safe. But they're you know, downsides, like

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* some people can. Can. Actually.

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* Kresge 502 Cart: you could even die from unnecessary surgery. Or, as Laurel mentioned.

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* Kresge 502 Cart: You know, side effects and treatment stress

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* Kresge 502 Cart: things like that.

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* Kresge 502 Cart: Okay? So

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* Kresge 502 Cart: they also differentiate between cancer-specific mortality and all cause mortality to propose looking at multi-cancer screening and alcohol mortality, to get at whether screening is saving lives, I think, is reductive.

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* Kresge 502 Cart: That's one of the arguments. Yeah, III think you have to add some useful.

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* This one here?

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* Kresge 502 Cart: Right?

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* Kresge 502 Cart: Yeah, could someone want to basically describe what you? I think? That's basically your point.

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* Kresge 502 Cart: You or anyone can describe, what's the main point? I mean, I think this is really the main point of of the slide of the paper.

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* Kresge 502 Cart: So we think even common cancers. like, you know, we think, yeah, that they're common breast cancer prostate cancer. But when you consider the number of people who who die from them.

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* Kresge 502 Cart: it's a relatively small percentage of the total. So an easy way to think of it is, I think Colon, cancer is a common cancer. Spend a lot of time studying it.

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* Kresge 502 Cart: But it's still 10% of cancer, just cancer deaths or colorectal cancer deaths. And then that's of all cancer and cancer is only a percentage of total deaths. So when you get down to it. You actually, even for pretty common cancers, seems kind of small. But

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* Kresge 502 Cart: I mean.

1:03:18

* Kresge 502 Cart: do you think this is a good way of looking at it? I mean it is in some respect. But you think it's missing something? Or is this the only way to look at it? Or is there a counter argument. If you're saying screening is actually more important than you're making out on this?

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* Kresge 502 Cart: Or do you think it's a pretty compelling argument?

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* Kresge 502 Cart: I just had a quick question. Yeah,

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* it wasn't clear to me if panels C and D are real data.

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* Kresge 502 Cart: or is it just a hypothetical suggestion? They didn't really talk about that in the method. So there's no really methods of the same

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* Kresge 502 Cart: if I had. So I know there's no screening trial to our knowledge that has 30 years of follow up after a moment. So I do think, they said, in 30 years, given the age, this is how many deaths we would expect. So I think that's okay.

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* Kresge 502 Cart: They got that gem.

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* Kresge 502 Cart: Yeah, it's interesting for the Colonel, I mean, it's hard to see. But

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* Kresge 502 Cart: I think the columns are about the same pipe. It's just so. They're actually

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* Kresge 502 Cart: like, you know. Yes, so so the screening is probably saving some lives. But is that offset by the I don't get breakfast. Normally. I'm sorry. I think the grabs normalized. That's why the cones are the same height.

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* Kresge 502 Cart: So it's like among all people that die, which percent would be due to death. So the world would be like all people that die. What's the risk of death?

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* Kresge 502 Cart: But after 30 years of follow up, you're saying 70% of the people would have died. So I don't think they realize that. And they just said, We expect, based on the outdate of these trials and 30 years of follow up that 70% of the population to be dead based on

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* Kresge 502 Cart: basic demographics. I think that's what they've done.

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* Kresge 502 Cart: Yeah. But you're right. There's no methods also. So it's hard to say exactly where they got these data from.

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* Kresge 502 Cart: Yeah, II think they really don't say

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* Kresge 502 Cart: where they got it.

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* Kresge 502 Cart: It's probably, but I think the point is still valid in a sense that it is true, because you do have data from the trials that have been done like prostate cancer trial

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* Kresge 502 Cart: for the the European study. What was

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* Kresge 502 Cart: like? How many do you remember roughly how many deaths from prostate cancer than total deaths. Yeah, you know, it was interesting because they didn't, even in that first publication, to even talk about total death

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* Kresge 502 Cart: at the first publication. No? Well, actually, I recall that the numbers I could be a bit off. But this is a trial that showed a benefit from screening on prostate cancer.

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* Kresge 502 Cart: They had something like

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* Kresge 502 Cart: like 70 deaths in the screening trial. And, like, let's say, around 100 in the control arm. But like there.

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* Kresge 502 Cart: the total numbers of deaths were almost identical. because I remember, these numbers may be off, but it's something like this. So this is total exams.

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* Kresge 502 Cart: So there were. So you know you have minus 30

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* Kresge 502 Cart: debt. So 30 30% reduction sounds impressive. But then, when you looked at the numbers now, you know.

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* Kresge 502 Cart: it was hard to tell like were there like 30 other deaths here. But that's out of 1,730. That's at least chance. So it's impossible to chance. But that's the main point. I think that if you're trying to do a trial to show

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* Kresge 502 Cart: a reduction in total mortality, even if there were like 30% reduction in prostate and no other death. So the trial was successful. The number is going to be too small for the total number

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* Kresge 502 Cart: to, you know, to look at a small reduction for the total. So so that's the main point, I think. Why.

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* Kresge 502 Cart: they would have to do like a humongous trial. But to get the numbers. But

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* Kresge 502 Cart: like so for colorectal, they estimated. Was it like 5.9 million?

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* Kresge 502 Cart: Here we go. Oh, yeah, this is.

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* Kresge 502 Cart: were anybody surprised by these, or having thoughts.

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* Kresge 502 Cart: the numbers they came up with here.

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* Oh, so

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* Kresge 502 Cart: one of this may equal other screen points. First, I think he talks about about Floss

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* observation studies. That's

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* Kresge 502 Cart: how how does 5 year over survival is not the accurate circuit marker how that is not accurately assessing, attributable to cancer screening cancer

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* Kresge 502 Cart: procedures that are associated that are also attributable in those studies. But

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* Kresge 502 Cart: one of the main things that I do from this table that he placed is that we want to show that maybe with all cancers or a movie cancer approach, we can lower the number

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* and get

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* Kresge 502 Cart: lower numbers that are maybe more rational to achieve certain

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* Kresge 502 Cart: period of time.

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* Kresge 502 Cart: Personally, Leon, I think that's wrong.

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* Kresge 502 Cart: Just because, as you mentioned, most of the patients with prostate cancer would not die of prostate cancer. Most of the patients with leukaemia would die with leukemia perspective to find everything in place, everything in the same basket for me. I've shown

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* Kresge 502 Cart: next step for a brief way to evaluate that

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* Kresge 502 Cart: But that's another. That's my advice.

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* Main problem with all at least putting everything in one basket

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* Kresge 502 Cart: and trying to decide that. I mean, he concluded.

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* Kresge 502 Cart: maybe we should do Rcts with multi-cancer studies to evaluate whether it is

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* Kresge 502 Cart: really beneficial

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* Kresge 502 Cart: or not. I think the result for that for prostate breast cancer or

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* Kresge 502 Cart: so, I'm not sure that's what I mean. That's what I do from this table, and I don't agree with it. But that's online.

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* Kresge 502 Cart: That's quite reasonable. Any other people that agree or have other.

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* Kresge 502 Cart: If people are not dying of pastures, they are going into fire. Another reason.

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* Kresge 502 Cart: Ok, so even though it be at all those deaths in together. Actually, the difference of dying cancer is really really small compared to

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* Kresge 502 Cart: countless of other reasons, whether it's like a disease or even an accident, because you have all class mortality. So also, that's why you would need such a big number of patients with cancer to actually test that. And it would be kind of similar to

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* Kresge 502 Cart: he rarely diseases. So it doesn't mean that because there's a really small number. And you're definitely gonna have enough power. But it doesn't mean that it does not exist. It does not benefit the patients

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* Kresge 502 Cart: and come up to your point also, though around the timing of death, like for colorectal cancer, you'd expect those to happen when, if you live to 5 years after diagnosis, you have a really good probability of surviving, whereas the other deaths might be 1020 years later. So it's also when you die, not only we're all going to die like we know for certain it's going to be 100% in that group at some point. But the timing of when you die in your life.

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* Kresge 502 Cart: Pretty similar.

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* Kresge 502 Cart: like statistics. And if you're going to throw all cosmetics, cancer is just like a small percentage. So you're gonna like, reduce your effect size in comparison to the population. And then you need more patients. But it doesn't like for me. Make the argument that you're not saving lives anymore.

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* Kresge 502 Cart: stronger. It's just like, as I said, like, everybody's gonna die. So of course, the difference that we have because everybody's gonna die and cancer. Especially prostate that happens later in life. So of course, people are going to be exposed to a greater risk of death.

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* Yeah. similarly, I think

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* Kresge 502 Cart: this paper just made me question a lot like, what is the purpose of screen? And it's in the name itself. It's like to screen for cancer. And so like when I saw the mortality, I immediately other people like government policies will say, like this is saving lives like the actual intention of cancer screening was to identify

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* Kresge 502 Cart: the cancer, and hopefully the quality of life and assigned treatments are clear afterwards. The whole point was to save lives that were like from

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* Kresge 502 Cart: the cancer, and not just

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* Kresge 502 Cart: more generally. I'll know if that makes sense. But

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* Kresge 502 Cart: I would love that to be debated as well. Yeah, no, that makes sense. Yeah. yeah. Sorry if I missed that.

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* Kresge 502 Cart: If you want to go identify.

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* Kresge 502 Cart: I may be missing this sense. It's also my hearing is better than I've left.

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* Kresge 502 Cart: you know, when they generalize. Oh.

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* Kresge 502 Cart: it may not be worth it to screw you with cancer, because you may just die in 10 groups. Anyway, I feel like it's a big ask of a patient to accept this uncertainty, but it may or may not impact your total lifespan would scare me a little bit high-risk groups that would be especially stressful.

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* Kresge 502 Cart: Yeah, there was little discussion on risk. Stratification

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* Kresge 502 Cart: makes sense to capture the cancer-specific mentality through measure. That is all caused

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* Kresge 502 Cart: just somewhere, like the idea that should be a different view

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* Kresge 502 Cart: where it's like death isn't beautiful. And the timing.

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* Kresge 502 Cart: please, that can be happy. And so why can I do so

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* Kresge 502 Cart: focus on other activities

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* because of cancer?

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* Kresge 502 Cart: Because you missed, for example, in a subgroup analysis. So if you were to do a whole cause mortality, and you assessed it.

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* Kresge 502 Cart: reveal enough effect. But if you were to look at it more specifically, you might have different groups that are hierarchy.

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* Kresge 502 Cart: This by doing this like very generic type of stuff.

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* Right? Yeah, yes, I actually had a question. So I realized that they proposed an Rct

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* Kresge 502 Cart: for the multi-cancer color test. And I was wondering, this doesn't seem very invasive. In the first place.

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* Kresge 502 Cart: doesn't seem like it's going to harm people. So why are they so focused on mortality

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* Kresge 502 Cart: it didn't. I don't see how that could hurt you.

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* Kresge 502 Cart: for the

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* Kresge 502 Cart: could do a lot greater. So you're saying that if it's not invasive. Yeah.

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* Kresge 502 Cart: like. And it's not going to impose harm on.

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* Kresge 502 Cart: Why is are they looking at all cosmetology

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* Kresge 502 Cart: on cause? Mortality is really a measurement that we look at. If procedures are in places

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* Kresge 502 Cart: you know. What's interesting to think about with. This is sometimes the first test is not invasive, but then what you have to do afterwards can be

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* Kresge 502 Cart: invasive can cause harm, can cause stress. So it's interesting. These multi-cancer detection assays. Many of them don't even aren't specific to it's elevated. You might have cancer. Do you have lung? Do you have blood, or do you have hidden? So then what you have to do afterwards? And then you find it biopsy. So there's these follow-up things that you need to do.

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* Kresge 502 Cart: Can. They are expensive, even though they're not expensive on an individual assay. If you have millions and millions of people

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* Kresge 502 Cart: pretty substantial, false positives, false negatives. So that's not the problem. Let's say 90%.

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* Kresge 502 Cart: It's

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* Kresge 502 Cart: and through true positive, like 90%. So we have 10% of all positive. These people are going to be biopsy because most of the people don't have cancer.

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* Kresge 502 Cart: And even from economic perspective, if they are trying to save some money. I think that this measure would actually cost more expenditure on the long run.

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* Kresge 502 Cart: because where people will have health positives. A lot of people will have to undergo further testing. And in the end we see it from a public health perspective. Cancer is not the biggest death based on their beta.

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* Kresge 502 Cart: So maybe we should be allocating most of the money to all of the releases.

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* Kresge 502 Cart: Yeah, it's interesting. I think cancer is still a major cause of death. But what they're saying is the proportion that's prevented by screening doesn't seem like a little bit screening is expensive to see if the screening is true.

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* Kresge 502 Cart: At least surgical treatment of more aggressive cancers tend to be riskier, more expensive, required ice, so there could be unintended with the screening of essentially tackling cancers at lower stages, where surgical management is a lot less risky, less expensive

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* Kresge 502 Cart: versus only identifying the cancers when they're metastatic and very aggressive, and suddenly requiring very expensive IC care or very risky procedures. They quoted 40%

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* Kresge 502 Cart: mortality after surgery is not cancer-related, but it tends to be riskier with higher stage cancer diagnosis.

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* And actually, just to that conventional horse I've just moved in. Then I'm sorry

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* Kresge 502 Cart: there's sort of this natural experiment, and I know we haven't done prostate cancer yet. But you know the the Us. Preventive Service Task Force, which is one of the groups that makes decisions or recommendations about screening came out strongly against prostate cancer screening in around 2,012 and then updated it to a more.

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* Kresge 502 Cart: You know, confusing recommendation of like talk to your doctor and make informed decisions. And so what you can see, these are are data from American Cancer Society, showing the up strong uptick across all racial groups in the incidence of cancers now being diagnosed, either locally advanced or metastatic. Already a diagnosis. So you can already see what's happening when screening rates are going down getting this up tick

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* Kresge 502 Cart: to your point. Exactly.

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* Kresge 502 Cart: Okay.

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* Kresge 502 Cart: yeah. The it I mean, I was. I don't know if this is a valid.

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* Kresge 502 Cart: Yeah, I was thinking in terms of like the the screening itself can cause like, strive if you get a screen detected cancer that eventually wouldn't cause death. You know, you're adding, like stress, unnecessary stress to the that person's life. Ii mean another aspect to that is like, let's say, you know, like, like 50 years ago.

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* Kresge 502 Cart: 40 years ago, you know, if you got cancer, it's like, it's almost okay, you know, right, burn your will. Whereas, like now, even though it's more like.

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* Kresge 502 Cart: you know, maybe maybe some cancer like there's lead time bias like that. But at least, if you have a diagnosis of cancer in most cases. Now, you know, maybe pancreatic. There's some exceptions definitely, but it's not like you have like 6 months to live. And that's it, you know. So II think you know it's I don't know if that's a good point you still like.

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* Kresge 502 Cart: It's better not to know or to just wait till the cancer is very advanced and you're diagnosed rather than being diagnosed 5 years earlier like that. So if it's not going to have a big impact on mortality. But I don't know. There are lots of

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* Kresge 502 Cart: subtle things like quality of life, how people react to different things. So. okay, are there any other. I guess we have 5 min left.

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* Kresge 502 Cart: I mean.

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* Kresge 502 Cart: So in general, like, what do you think like

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* Kresge 502 Cart: of their I mean, I mean, I did you

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* Kresge 502 Cart: think that they have a good point or a valid point in general? Or.

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* Kresge 502 Cart: yeah, something that I'm trying to understand is, what about perfect detection, or as cancer state. Is it possible?

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* Kresge 502 Cart: Right? And so would you argue that just what it is? If you die of something else or the cancer can be enough.

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* Kresge 502 Cart: Is it more like a question of individual versus population level benefits?

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* Kresge 502 Cart: Yeah, I mean, I think age is another

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* important aspect. And for

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* Kresge 502 Cart: for some screening tests. Like prostate and colorectal. I'm not sure about breast. There's a cut point where you usually don't recommend doing screening

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* Kresge 502 Cart: for prostate Psa. Was it beyond age. 75 or 80.

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* Kresge 502 Cart: something like that. So, yeah, I mean, you are like.

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* Kresge 502 Cart: like a lot of these statistics are population based. We're talking first and years. But

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* Kresge 502 Cart: if you look at it from an individual perspective, it can be quite different. So sometimes, one way, statistics were there.

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* Kresge 502 Cart: But sometimes you'll read a statistic like, Oh, if you exercise, you'll gain on average

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* Kresge 502 Cart: 2 years of life. And the way psychologically, some people think, boy, Ok, maybe I'll die at 92 instead of 94, maybe I'd prefer to die in 92 than 94. They kind of think of it like everyone is getting the same small effect. But if you think about it as

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* Kresge 502 Cart: well, like another way to think of it is like 2 out of 10 people will die 10 years prematurely

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* Kresge 502 Cart: like, are you willing to take that risk? Ok, maybe you don't exercise, and maybe it won't perturb you like that. But there is a 20% chance that you'll die 10 years earlier. To me that seems actually more

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* Kresge 502 Cart: compelling than saying, like 2 years, adding one or 2 years to everybody in the whole population. So person years is useful for statistics.

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* Kresge 502 Cart: I don't think it's useful to a way to think about risk

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* from an individual perspective, how you would make a decision. Yeah.

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* Kresge 502 Cart: no? Sorry. Yeah. I was struggling with the same thing. But I had a question also about over diagnosis.

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* Kresge 502 Cart: I should start looking at like how that's

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* Kresge 502 Cart: determined that something would not eventually go on to cost mortality. That's kind of another similar as individual versus population. You can't tell on an individual basis.

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* Kresge 502 Cart: If it's over diagnosed, you can just tell on the population because you have a lot more cancers diagnosed by a screening test. But reduction on mortality was, let's say, modest, pretty low. So from that population perspective, you know that.

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* Kresge 502 Cart: Yeah, if you knew those people that weren't going to die anyway. Yeah. But that's like a valid point is from an individual perspective. Unless you have better ways of looking at the histology and telling

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* Kresge 502 Cart: which cancers are really important. It's like Laura, like talked about, you know, pseudo cancers. But that's basically what that means is, histologically, they look like a cancer, you know just by looking at the features, say, yeah, this looks like all has all the definitions from cancer. But

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* Kresge 502 Cart: it's possible that if you knew exactly the mutations, and that some of them were very, very unlikely to progress. That would be kind of like a Holy Grail, you know, if you not just told a person to have cancer. But oh, this cancer is won't progress. If you knew that, then say, don't have cancer, but

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* Kresge 502 Cart: we're not there yet.

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* Kresge 502 Cart: Yes. Do you think that early detection for most people can extend the number of volume life years? Or does early detection sometimes just spend the amount of time that someone's going to be experiencing treatment

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* Kresge 502 Cart: their light years

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* regardless of screen.

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* Kresge 502 Cart: Yeah, II mean, I think that's that's sort of the question like we don't know, like, on an individual basis, like for some people, it may actually be benefiting other people.

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* Kresge 502 Cart: They would die at the same day.

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* Kresge 502 Cart: Or is it just like all of that time, you can detect it so early. You're going to be undergoing treatment, and that's decreasing quality of life, or all of those remaining 10 years.

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* Kresge 502 Cart: III don't know. I mean it. Probably I mean, it's a great question. It probably depends on answer.

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* Kresge 502 Cart: I don't know. Some more clinical people might have better answer. But

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* Kresge 502 Cart: yes.

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* Kresge 502 Cart: So basically, what would have to happen is even as a person, let's say.

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* Kresge 502 Cart: died at the same, you know, but you know that same day, but the early detection they were treated, and it avoided some of the therapies that they would have gotten

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* Kresge 502 Cart: had. They were diagnosed with more of a man's gauge.

1:30:06

* Kresge 502 Cart: but they are still theoretically dying the same day, so maybe they're still getting some.

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* Kresge 502 Cart: It's not like they do perfectly fine, and then just guide. One day they probably still have a lot more fish, but they could be avoiding.

1:30:17

* Okay.

1:30:27

* Kresge 502 Cart: 17. Daily basis discussion with the patient is based on patient, personal,

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* Kresge 502 Cart: patient expectation and lots of care. I mean, there is no study. That's exactly what

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* Kresge 502 Cart: symbolize it with that.

1:31:04

* Thank you. I think we're over. Thank you. I think we covered most of the important facts.

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* Kresge 502 Cart: Any any final comments or

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* Kresge 502 Cart: great thanks, everybody. We'll see you on Thursday for the prostate cancer lecture. And then just a reminder you're doing office hours today at right now and in room.

10

* Kresge 502 Cart: Stop, stop prosecutor

0:15

* technology. Conrad is a physician, scientist trained in internal medicine, received his mph here at the Harvard School of Public Health, and has been engaged in really very innovative research across the pathogenesis and cancer continuum and prostate cancer.

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* and has given this lecture in our class. Now, this is your third year doing it, and really excited that he's come back. He's an assistant professor, both at Harvard Medical School and here at the Harvard school of Public health. So, however, thank you so much. We're delighted to have you have your lecture today. Thank you, Lorelei, and welcome everyone. If you've ever been to Rome, not the Rome in Italy, but Rome with the Vatican, and lecture to the Pope

1:04

* Kresge 502 Cart: about cat cynicism. That's how I feel when I lectured to these 2. So I'd love to talk with you today about 3 fundamental things of prostate cancer. That's the first 3 things on this slide here, and that is some clinical features.

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* Kresge 502 Cart: what is prostate cancer? And then we'll talk about the descriptive epidemiology. How much of prostate cancer is there, and particularly racial disparities in prostate cancer. We'll talk about inherited genetic factors, which are a big contributor.

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* Kresge 502 Cart: And then, in the second part, if you will, are the things that talk about, what can we do about this? And the first one is risk factors and primary prevention. The second part is around screening Psa screening, and that we always need to think about Psa screening when we talk about prostate cancer. And then the last part will briefly talk about

2:13

* Kresge 502 Cart: cancer, survivorship and cancer survival and treatment as an important contributor to the burden of prostate cancer and to the burden that men with prostate cancer face. I would like you to interrupt me

2:34

* Kresge 502 Cart: at any point. I will ask you questions if you don't ask me. But please please still jump in right away. So let's talk about what prostate cancer is what is the prostate? The prostate is probably the most boring organ in the human body, and I mean this, after studying this organ or

2:50

* Kresge 502 Cart: for 10 years. So it's hidden in the pelvis. It's so unimportant that half of humanity can very well, and maybe even better, do without it. So

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* Kresge 502 Cart: it's next to the bladder next to the rectum, and not a very interesting spot of the human body, and we would not be talking about this organ ever, almost ever in medicine if it wasn't the site for cancer. And one of the most common cancers in

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* and

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* Kresge 502 Cart: in people. So that's really the most important thing about cancer

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* Kresge 502 Cart: is. But the prostate is cancer. There's basically 2 other reasonably common conditions about the prostate that ever come to to light. As the prostate grows with age. So it's

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* Kresge 502 Cart: not uncommon reason for people not able to pee, because the urethra goes directly through the prostate and the other condition there is is prostateis, but other than that, it's

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* Kresge 502 Cart: such a common place for cancer to originate.

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* Kresge 502 Cart: But, we talk about prostate cancer. There are 2 dimensions that are important when we talk about it. One is.

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* Kresge 502 Cart: how big is the cancer and how much is there? So that's staging? That's similar to what you see in in other solid tumors. And we'll also talk about grade. Which basically means, how does the tumor look like under the microscope? So for staging, we're talking about 3 different

4:42

* Kresge 502 Cart: facets of of stage. The first one is the tea stage. So that talks about the primary tumor. So there we're talking about this walnut sized organ that the prostate is, and

5:02

* Kresge 502 Cart: T. 3, and which isn't depicted here, basically say, how big is that cancer within the prostate, or how much has it already grown slightly beyond the prostate. So a would, for example, be invading the bladder, which is an organ that's sitting right next to the prostate.

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* Kresge 502 Cart: So here we're really talking about cancer in the prostate. The big difference is whether or not cancer has spread to distant organs. As with other solid tumors, so the other components of Tnm staging is whether that termer has spread to lymph nodes.

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* Kresge 502 Cart: This is

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* Kresge 502 Cart: more challenging to talk about and not as important as the third part of Tmm's brain staging, which is distant Midhouse disease. So

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* Kresge 502 Cart: other parts of the body, being affected by metastases of prostate cancer, are the most common site

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* Kresge 502 Cart: of metastasis

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* Kresge 502 Cart: from prostate cancer is bone. So there are basically 2 common clinical presentations of prostate cancer, or 3. The first and most common one is

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* Kresge 502 Cart: no symptoms at all, and the cancer is detected by Psa screening. And that's why we'll need to speak about Psa screening for sure

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* Kresge 502 Cart: other than through a lens of prevention. The second one is, you can imagine this tumor growing and pressing on the Urethbrasine, and the third, which is a sign of distant metastases, is the tumor already having spread beyond the prostate, and those

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* Kresge 502 Cart: those presentations are really due to pain and commonly back pain. So the classical presentation is

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* Kresge 502 Cart: elderly men coming to an emergency room with trouble, peeing, and back pain, who hasn't seen primary care for a few humors, and that would then be metastatic, prostate sort of as the classical vignette to picture a person for you.

7:12

* Kresge 502 Cart: But again, the majority of cases, at least in the United States nowadays, are of T stage onec. Not metastatic, that are detected by Psd. Springs, so by blood tests only, and are not even culpable on the organ. Why is staging so important? If we look at relative survival

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* Kresge 502 Cart: in the

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* Kresge 502 Cart: in 5 years after diagnosis for those 70% of patients diagnosed with localized prostate cancer and smashing proportion with regional prostate cancer. So nodal positive lymph nodes, the relative survival is

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* Kresge 502 Cart: close to 100%, or it can actually be greater than 100%. Does everybody remember when Michelle and Colleen talked about different measures of survival, what relative survival is, and how it's different from, say, just looking at survival as a concept. Do you remember what relative survival is? Exactly, and why it could be greater than 100%

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* Kresge 502 Cart: sorry to interrupt. But

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* Kresge 502 Cart: it's weird right. Why would survival be greater than 100%. It can only live once, I guess.

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* What are they doing in relative survival and calculating? What are they comparing

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* Kresge 502 Cart: survival, too, that it could be bigger than 100%.

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* Kresge 502 Cart: I see some of you wanting to say something. Yeah.

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* Kresge 502 Cart: that's a free individual. because of some people screamed out.

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* so that's why I did.

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* Kresge 502 Cart: Yeah, great. I'll just repeat what both said. So basically, relative survival is a comparison to people typically of the same age and in sex, or what the cancer registry or courts

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* Kresge 502 Cart: over the 5 years. So it really depends on who is diagnosed with cancer. So it's comparing to

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* Kresge 502 Cart: to basically people at the same age. And so that means, if people who get a diagnosis of prostate cancer are more healthy.

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* Kresge 502 Cart: the relative survival will be better, even though they have cancer. And we'll talk about these are cancers, localized prostate cancers. They tend to be very indolent. So it's really about

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* Kresge 502 Cart: different people getting getting diagnosed.

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* Kresge 502 Cart: but not to forget. And we'll see this in just a bit. The survival of metastatic prostate cancer

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* Kresge 502 Cart: is poor and continues to be poor, and

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* Kresge 502 Cart: there is no curative therapy for metastatic prostate cancer and metastatic prostate. Cancer is a big public health burden. So this is one of the fundamental challenges that we face with this cancer is

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* Kresge 502 Cart: that

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* Kresge 502 Cart: relative survival of people with localized prostate cancer is very, very high, but it is still bad for people with metastatic prostate cancer.

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* Kresge 502 Cart: So I promise there is a different second aspect to sort of one of the 2 big perspectives on prostate cancer. And that is grade. This is a slide that's really for your reference. Nobody will ask you about how you define Gleason grade and score.

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* Kresge 502 Cart: but it basically is on a visual description on how the tissue looks like under a microscope and typically prostate tissue looks organized. It's a gland that has a function. This organ that is so boring does have a function, it produces

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* Kresge 502 Cart: a fluid that helps with sperm. And but that is really

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* Kresge 502 Cart: the organizing pattern of this tissue is really very clear, and as cancer progresses or as cancer initiates and then progresses through its grades, the tissue becomes increasingly disorganized.

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* Kresge 502 Cart: So that's what visually this system is is capturing nowadays, we would be creating an AI algorithm that looks at the tissue and then picks up what is bad about it. This patterning was actually created by a pathologist, looking at

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* Kresge 502 Cart: many cases and sort of deciding visually. Oh, these ones look bad, and these ones don't look bad, and he gave them numbers, and his name was nieces, and that's why Lesen's words from the and and is held up, and is actually an even stronger predictor of prognosis and prostate cancer than stages, or, you see in that stages

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* Kresge 502 Cart: is a strong predictor.

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* Kresge 502 Cart: So now I have a lot of questions for you, one big one very important graph to to look at, and I'm curious about your thoughts. What you make out of these numbers that I'm showing you here. What I'm showing you here are is the prevalence of prostate cancer at autopsy.

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* Kresge 502 Cart: of men who died from other reasons than prostate cancer.

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* Kresge 502 Cart: So I lost

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* Kresge 502 Cart: because the numbers are smaller, give use it. So the scale here goes from 0 to 60%.

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* Kresge 502 Cart: And these are the 3 bars are for different racial categorizations.

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* Kresge 502 Cart: What do you make out of this data. And what do they tell you about prostate cancer? I'm curious about your thoughts. There's so much that we can read into this

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* Kresge 502 Cart: right? So again, none of these people had a diagnosis of prostate cancer. Exactly. So that is important. Thank you, Laura. So these people did not have a diagnosis of prostate cancer in life. They died from car accidents, they died from heart attacks, they died from anything but prostate cancer, and then they had an autopsy, and I'll just look at their prostate tissue and decided whether or not there was histologically tumor present in in that.

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* Kresge 502 Cart: Yes, significant in the US. White European populations between 29 to 30 to 39. Which is interesting.

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* Yeah.

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* Kresge 502 Cart: Great observation. Why do you think that is, or what could be done out there? I would assume. It's just

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* chain also

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* Kresge 502 Cart: issue.

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* Kresge 502 Cart: Yeah, I mean, that's very hard to know from these graphs. This is one of the most important points, the prevalence of toxic cancer at autopsy already goes up to very high levels

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* Kresge 502 Cart: for 30 to 39 year olds. So a lot of us

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* Kresge 502 Cart: quarter to a third is the prevalence in an age group where basically nobody gets diagnosed clinically with plastic cancer.

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* Kresge 502 Cart: Yes, so I can tell with you from the regardless of race.

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* Kresge 502 Cart: And they erased themselves, having prostate cancer.

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* Kresge 502 Cart: basically age.

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* Kresge 502 Cart: And, second, that African-americans tend to have a larger percentage of prostate cancer.

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* Kresge 502 Cart: not offering the treatment or the screening tools in that population. That's why they are having

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* Kresge 502 Cart: diagnosis. Yes, so great. 2 very important observations. One is, I'm

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* Kresge 502 Cart: there is a strong age relationship. The first part is exactly what your classmates already said. Already, at a very young age the prevalence is very high, but then there's a strong increase with age in addition to that, and then you point it to

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* Kresge 502 Cart: differences between these race calculation that we often use

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* Kresge 502 Cart: on. And one explanation could be, there's

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* Kresge 502 Cart: we're sort of in us white and European patients. Here, we're sort of selecting away the cases versus in the black group here who haven't diagnosed them in life. So that's an interesting question.

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* Kresge 502 Cart: yeah, what do you think? What could? What could be going on there?

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* I mean, it could just be that.

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* Kresge 502 Cart: And then.

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* Kresge 502 Cart: second, maybe we are maintenance

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* Kresge 502 Cart: right on.

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* Yeah. So those are 2 important contributors. I like that. You're starting with the first. Yes, life expectancy is a lot shorter

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* Kresge 502 Cart: in black men in the United States. So that's one part of the explanation. The other one is, there were just fewer studies also. So the data weren't sufficient to come up with reasonably

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* Kresge 502 Cart: precise estimates for that group. But

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* Kresge 502 Cart: prostate cancer. To make one thing clear, prostate cancer does not disappear over age of 80. That's definitely not the message of this slide, and it's also not that they've all died from prostate cancer.

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* Kresge 502 Cart: Other thoughts about this graph

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* Kresge 502 Cart: great points that will be

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* Kresge 502 Cart: talking about.

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* Kresge 502 Cart: I'll show you one other annotation here. Yes, great.

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* Kresge 502 Cart: Hmm.

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* Kresge 502 Cart: oh, yeah, yeah. Great moment. Yeah. So this is a, this is actually a meta-analysis. So this isn't. This isn't just one single original study that I pick because it is really a pooling of

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* Kresge 502 Cart: Already the available autopsy studies that were available up until, like 10 years ago, there might be a few additional ones. I know there's one being done now. But yeah, racial categories are always

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* Kresge 502 Cart: question and yes, leaving out on other groups if more so

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* Kresge 502 Cart: great. So the other part annotation that I wanted to give here is on the lifetime, risk and lifetime.

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* Kresge 502 Cart: The left side of this slide shows you what we could find if we auto seed everyone, we're not doing that.

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* Kresge 502 Cart: So of these huge prevalence numbers here the majority will remain undiagnosed.

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* Kresge 502 Cart: And what I'm showing you on the right here with that 13% lifetime risk is this is the cumulative incidence over a lifetime of being diagnosed with prostate cancer.

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* Kresge 502 Cart: So the big take home message, here is there is way, more plastic cancer that could be diagnosed than what we are, even currently with very intensive screening diagnosed.

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* Kresge 502 Cart: and we'll come back to whether that is good or bad. So let's focus a little bit more on how prostate cancer looks like in living people, because at the end of the day that's a little bit more important for public health than what we could be labeling people with.

20:03

* And I'd like to show you

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* Kresge 502 Cart: interesting overview of the global burden of

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* Kresge 502 Cart: prostate cancer. This is prostate cancer incidence. So this is new diagnoses. There are 1.4 million. About incident, prostate cancers globally.

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* Kresge 502 Cart: with very strong differences

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* Kresge 502 Cart: by both our continent and by a country with particularly notable. Lower incidence rates in Asia. I think that's the most important pattern to to point out here.

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* Kresge 502 Cart: And then for prostate cancer mortality a different.

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* Kresge 502 Cart: broader picture, with particularly notable high mortality rates

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* Kresge 502 Cart: in sub Saharan Africa and in the Caribbean. and again.

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* Kresge 502 Cart: relatively low mortality rates in Asia.

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* and when we look at different.

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* Kresge 502 Cart: a slightly subcontinental level breakdown. We see that prostate cancer, incidence and mortality

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* Kresge 502 Cart: don't for one, differ dramatically between different regions, and that they, as you can see don't track very well with each other.

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* Kresge 502 Cart: and what we'll be seeing. Why, why, that might be. Let's look at the United States for a bit.

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* Kresge 502 Cart: So these are the prostate cancer incidence trends in the United States. And here we're down to 2 racial groups with an combination of

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* Kresge 502 Cart: ignoring Hispanic ethnicity.

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* Kresge 502 Cart: or some what could be going on for these 2 graphs over time. What is happening there?

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* Kresge 502 Cart: That's a badwa. But we're seeing there.

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* Kresge 502 Cart: Yes.

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* heard in Sweden.

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* Then it's possible.

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* Kresge 502 Cart: Yes, great. So what we're seeing the big

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* Kresge 502 Cart: thing here is, we see a jump in the incidence. So in the number of diagnosed cases every year in both racial groups, slightly differently. When Psea screening came around in the early. And we'll talk more about what screening, how that entered.

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* Kresge 502 Cart: What's what could be going on here in more recent years?

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* Kresge 502 Cart: Any idea?

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* Kresge 502 Cart: Yep, maybe you're more valid test. So that's also true.

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* Kresge 502 Cart: Yeah, that would.

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* Kresge 502 Cart: That is something that people are working on.

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* Kresge 502 Cart: Unfortunately, it's not quite what we're seeing, what we're seeing here yet. We hope to see better, smarter testing in the next few years. The Psa test

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* Kresge 502 Cart: so far. To mention the Psea test will remain part of the mix. So the Psa test is actually not a bad test, but it's not been used very smartly. But what people are doing exactly to your point is, they're integrating information from additional tests, from genetic tests, from imaging tests such as Mris.

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* Kresge 502 Cart: or they diagnose people with prostate cancer, with the idea being to avoid diagnoses of

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* Kresge 502 Cart: of cancers that don't need to be diagnosed and

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* Kresge 502 Cart: and diagnosing people who do need a diagnosis or would benefit from a diagnosis because they would benefit from treatment in order to avoid that risk of progression to metastatic prostate cancer that has such a high risk of of death. So what you're seeing here is actually changes in clinical practice guidelines here

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* Kresge 502 Cart: around 2,009 on the US. Preventative services task force. That is not the only body that makes cancer screening guidelines, but it's the body that makes cancer screening guidelines that affect reimbursement. They came out with a recommendation against prostate cancer screening. So what you see here is just less screening.

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* Kresge 502 Cart: And in 2015

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* Kresge 502 Cart: they changed course and recommended prostate cancer screening again. So then, you see incidents going up again.

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* Kresge 502 Cart: So those are really the major. Of course there's more going on here, but those are the major factors in fluids.

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* Kresge 502 Cart: These were mortality trends. What do you think is going on there?

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* Kresge 502 Cart: Yes.

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* Kresge 502 Cart: musical

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* 2,000.

26:02

* Kresge 502 Cart: And then I guess metal truth.

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* Kresge 502 Cart: Umhm, so that so the first part is very interesting. Basically, it means, yes, there is screening here. And that leads to more people getting a label of prostate cancer and having a chance to die from it. But at the same time it also meant that

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* Kresge 502 Cart: more, that we started diagnosing and treating people whose cancers would have later progressed to metastatic prostate cancer. And they would have died from that. So what we're seeing this continued decline ever since is actually an effect of Psa screening. So we're seeing the benefit of Psa screening in these decreasing rates here.

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* Kresge 502 Cart: Anything else? That's apparent. Very

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* maybe jumping at you when we look at the 2 curves.

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* Kresge 502 Cart: others on. There's the stark difference between the black and the curve for black and for for white men here for the United States, and we see that the uptake of that the changes weren't as dramatic in the in the lower.

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* Kresge 502 Cart: And

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* Kresge 502 Cart: we're we're more notable in in the in the back group.

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* Kresge 502 Cart: And we're looking at an absolute scale here. The absolute number of deaths

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* Kresge 502 Cart: was a lot higher that were prevented among flattened. So I think that's awesome. What we see overall similar similar trends. But differences in absolute magnitude.

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* Kresge 502 Cart: so changes in prostate cancer mortality. By the way, don't just have something to do with screening. These are data from a bunch of European countries. Over a century before Psa screening was available. And, as you can see, there are huge changes actually up to 5 fold in the same country of prostate cancer mortality rates.

28:02

* Kresge 502 Cart: Why could that be

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* Kresge 502 Cart: curious about the answers? Because I don't know the answer. And

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* we have 2 people who know answers. They're shaking their heads, too.

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* Kresge 502 Cart: so we don't totally know. But let's think about together. What? Why could this be? What could? What could be going on here?

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* Kresge 502 Cart: And we see such changes for other cancers, too, not always in the same direction, with the same patterns, though

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* Kresge 502 Cart: the curve for breast cancer looks actually very similar. The curve for stomach cancer looks very different. It's just gone down or the curves for stomach cancer, I should say

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* Kresge 502 Cart: I'm just guessing is previously like in my team

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* Kresge 502 Cart: for 2010, like very few prostate cancer, are actually diagnosed. And so as your diagnoses sensitivity or or

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* Kresge 502 Cart: becomes more accurate and more people get diagnosed, they die from prostate cancer.

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* Kresge 502 Cart: That is a great explanation. And that is certainly one. I think that is one

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* Kresge 502 Cart: reasonable contributor, that

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* Kresge 502 Cart: it's always a problem in these long-term comparisons. Basically medical care changes our ability to even diagnose it

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* Kresge 502 Cart: did change even the diseases that we think exist. Change over time because we are learning of new diseases. We're splitting up the same disease into into more than more and more categories. So I think that's a great explanation. It may not be the entire explanation and to to come back to that example of gastric cancer at which I had the slide.

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* Kresge 502 Cart: Everything goes down so people sort of we wouldn't need to say. People knew how to diagnose stomach cancer, but they didn't know how to diagnose. Prostate cancer is a cause of death. So it's certainly contributing.

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* Kresge 502 Cart: But it may not be the only explanation other.

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* Kresge 502 Cart: Could there be other explanations? What do you think?

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* Kresge 502 Cart: I'm actually just staring at my next slide here, which is to your point. So maybe let's look at this together. And this is about how well do we actually know that someone died of cancer?

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* Kresge 502 Cart: And well.

31:07

* Kresge 502 Cart: this is a study that tried to find this out. So. autopsies. I already showed you one autopsy study. This is a town on the eastern border of Germany, called Garlitz, on

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* Kresge 502 Cart: in 1,987. In this town I actually grew up an hour away from. So in 1,987. There were 1,060 people who died in that town of Gurlitt. I think there were about 100,000

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* Kresge 502 Cart: people, but

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* Kresge 502 Cart: And so there were 1,060 people, and out of those 1,060 people they were able to do an autopsy on 1,023. So 97%. So that's how many autopsies do we do? Currently, in the United States, when people die here, what percentage of people get an autopsy.

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* Kresge 502 Cart: Or let's say, how many don't about 97%. Actually. So it's something that we don't do any longer. And of course they did that here, basically for research purposes. But the autopsy rates were a lot higher back then.

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* Kresge 502 Cart: So let's exactly to your point. Did these people actually die of prostate cancer were able to to find that we're able to to to define that. So what they did, they tabulated what the death certificate said, what people were dying from, which is our usual cause of of cancer, mortality data. And then in the columns here, they're showing you what the cause, what the category of causes of death was based on

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* Kresge 502 Cart: on the autopsies that they did for the purpose of the study. So there were 199 people who were said to have died from neoplasms on their death certificate. So basically, if I'm

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* Kresge 502 Cart: whom cancer and you would assume from metastatic cancer. Of those 199 people, 178 were found to have died of cancer on their autopsy.

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* Kresge 502 Cart: So actually a pretty high, positive, predicted value.

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* Kresge 502 Cart: considering like this is why do I look on

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* Kresge 502 Cart: they didn't have computer tomography. They didn't have a lot of. There was no Psa. There were lots of things this in just pass it, of course, but there was lots of medical care that wasn't available.

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* Kresge 502 Cart: There were 30 people here who were said to have diagnosed have died of heart attacks on near embolisms and so forth. And they actually died of cancer based on the autopsy. So the sensitivity

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* Kresge 502 Cart: of the death certificate wasn't perfect. So there was actually more cancer. And it's often been described that cardiovascular disease in older people gets slightly over diagnosed, and these discrepancies that they saw were particularly

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* Kresge 502 Cart: oh.

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* Kresge 502 Cart: so to your point, there is definitely room for some of the differences over time if medical care gets more accurate to explain these things. But it doesn't seem like we're not seeing that the majority of cancer causes on the death certificate were wrong, at least in the in one town in Eastern Europe.

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* Kresge 502 Cart: Great! Let's quickly look back at these. What else could be changing over time?

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* Kresge 502 Cart: Yeah, yes, forward

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* Kresge 502 Cart: compared. I know this is decades ago, but compared to other countries

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* Kresge 502 Cart: in Europe, and I know the comparison is not really fair to the Us. But how does determine

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* Kresge 502 Cart: the cause of death? How can you intervene to the Us. Is it better or worse? Just to kind of generalize, although it's hard, but just.

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* Kresge 502 Cart: that's a good question, and a very, very tough one, because in order to have a good answer for you, I think we would actually need this type of study?

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* Kresge 502 Cart: Yep, yeah. And vice versa in a country that might be lower resourced. And so how good is it there

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* Kresge 502 Cart: having that comparison.

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* Kresge 502 Cart: seeing if it's like that there that help me in other countries that are not like, you know. And then, even like in a country like us, if you're diagnosed, maybe, or if you die at mass, general Hospital versus if you die in a local community hospital, is that the same?

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* Kresge 502 Cart: I don't know. Maybe maybe not.

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* Kresge 502 Cart: I wish I had a quantitative answer to you. I have anecdotal answers for this

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* Kresge 502 Cart: death. Certificates filling them out are not necessarily anyone's primary priority, because

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* Kresge 502 Cart: physicians typically care about living patients and people die

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* Kresge 502 Cart: in the middle of the night in the intensive care unit, or wherever it may be, but not necessarily. The death certificate may not reflect the entirety of what we know about them medically, even in life. Then, of course.

36:38

* Kresge 502 Cart: yes, in theory, Germany, a well resourced country and so forth. This was Eastern Germany before the reunification services behind the Iron Curtain. There wasn't a lot of technology, it was medical training, but there were no American textbooks or something, so it may not be the Germany of of today. And then, even in the Germany today, I can tell you that

36:56

* Kresge 502 Cart: for grandparents, I can tell you that Alfor died with a cause of death that was completely wrong. I don't know. That's an anecdote, but even in a very highly resourced country. So

37:21

* Kresge 502 Cart: yeah, for example, what happens like those patients cancer.

37:37

* they have like high.

37:43

* Kresge 502 Cart: That's how they work.

37:46

* Kresge 502 Cart: Yeah, yes, very good. So we can spend the next

37:49

* 90 min on the classifying causes of death. But this is exactly people die because of cancer, because cancer creates havoc in the body, and cancer creates havoc in the body in terms of blood clots, for example, and that causes a polyamorous one. That's what people ultimately die of, but that is the

37:56

* Kresge 502 Cart: immediate cause of death, and it shouldn't be the one on the death certificate, because people would not have had. The argument is, people would not have had

38:17

* Kresge 502 Cart: this this black client had they not had the cancer. So the underlying cause of death is actually cancer. And across countries to your point about comparisons. That's how ICT classifications of death are to be performed, says the who. So that is always the underlying cause of death.

38:27

* Kresge 502 Cart: So, for example, during the COVID-19 pandemic. There was a lot of arguments about is COVID-19, a common cause of death, and the argument was well. These people were dying actually of heart attacks, while they also had Covid when they were in the hospital. Yes, but they wouldn't have been in the hospital on a ventilator and then gotten a heart attack, had not had Covid so who again said, Covid, is the cause of death, because it is the underlying cause of death.

38:53

* Kresge 502 Cart: Great I didn't expect to talk about Covid. So let's get back to prostate cancer and get back to the United States in 2,023. I updated everything about this slide except the title, and it should be 2024, those numbers actually, so these are estimates actually are from based on data from a few years back.

39:24

* Kresge 502 Cart: about 300,000 people are expected to be diagnosed with prostate cancer in the United States this year, which is about almost a third of all new cancers in men.

39:49

* Kresge 502 Cart: and about 35,000 deaths are expected this year, which is about one in 9 of every death from cancer. So both for incidence and for mortality, a major bird. So those were the population statistics and individual level statistics is that 13% lifetime risk that I quoted earlier and one in 40 risk

40:03

* Kresge 502 Cart: of dying from prostate cancer.

40:32

* Kresge 502 Cart: So which also means these numbers also trade translate to a substantial prevalence. There are 3.6 million people in the Us. Right now. Will have a diagnosis of prostate cancer, and who may have been completely, successfully treated, and may never see their

40:36

* Kresge 502 Cart: deal with prostate cancer again. But we'll still undergo monitoring and so forth. But about 100,000 to 150,000 of them. We don't exactly know how many

40:56

* Kresge 502 Cart: are actually living right now with metastatic prostate cancer.

41:08

* Kresge 502 Cart: So, coming back to our racial disparities, and I think that was hard to overlook in the previous slides, even from trends. These are again

41:14

* Kresge 502 Cart: racial categories. Now we're at 5 racial categories, the ones that the census

41:24

* Kresge 502 Cart: users, plus a group separately for Hispanic. And what you see is

41:31

* Kresge 502 Cart: very, very strong disparities in prostate cancer mortality. If White were the reference group than the mortality rate in black men were 2.1 fold greater. But if Asian were and Pacific Islanders in one group were the reference category. Then we're talking about a fourfold difference. So

41:38

* Kresge 502 Cart: so huge

42:03

* Kresge 502 Cart: disparities. And they're only in gastric cancer. As big as

42:05

* as a prostate cancer.

42:12

* Kresge 502 Cart: So why is that, and the next heart is about inherited genetics. That is not to say that inherited genetics are the only cause.

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* Kresge 502 Cart: And, in fact, I'd like to look together at this

42:27

* Kresge 502 Cart: graph here together with you, and see what we make out of these numbers here together. These are.

42:34

* Kresge 502 Cart: This is a great example of a migrant study where. looking at prostate cancer incidence before psa screening messed up the picture

42:42

* Kresge 502 Cart: prostate cancer incidence between.

42:57

* Kresge 502 Cart: I've been in Japan

43:02

* Kresge 502 Cart: the first generation of migrants to Hawaii, the second generation and white Hawaiians.

43:05

* Kresge 502 Cart: And we're seeing that for prostate cancer on the right and then stomach and breast cancer in the left and in the middle.

43:17

* Kresge 502 Cart: what do these numbers tell you? How do you interpret them?

43:30

* Kresge 502 Cart: Let's start with a stomach cancer on the left, because that is the most clear cut.

43:52

* Kresge 502 Cart: Yes.

44:04

* migration.

44:10

* lifestyle factors.

44:15

* Eric.

44:19

* Kresge 502 Cart: Yeah, I'm I'm walking

44:22

* Kresge 502 Cart: complex.

44:28

* So

44:35

* Kresge 502 Cart: great summary of the data. And you're exactly pinpointing 2 of the Major, I don't know competing, but major explanations. One is. Migrants

44:37

* Kresge 502 Cart: a generation later are genetically the same as the country they're coming from. As a population even 2 generations more than that.

44:53

* Kresge 502 Cart: So there must be something that's not genetic that's changing. And yes, we know each pylori infections are

45:04

* Kresge 502 Cart: the major modifiable factor for stomach cancer with hygiene and more antibiotic exposure on immigration. That is one of the contributors there

45:14

* Kresge 502 Cart: and then there are probably genetic differences. What about breast and prostate. There's one thing that I don't want to get you too tripped off. Is this difference here between these 2 bars here? That's maybe hard to interpret.

45:31

* Kresge 502 Cart: We're seeing the opposite pattern. We're seeing that on immigration to the United States

45:55

* people without a change in their genetics so suddenly, you have a substantially higher risk within a generation

46:02

* Kresge 502 Cart: than white Hawaiians.

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* Kresge 502 Cart: At the same time, even within 2 generations, for both breast or prostate cancer.

46:15

* Kresge 502 Cart: the levels of risk don't reach that of the

46:23

* Kresge 502 Cart: of the other archbishop.

46:29

* Kresge 502 Cart: That is summary that

46:34

* Kresge 502 Cart: everyone more or less could agree with.

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* Kresge 502 Cart: Okay, then let's try to understand why that could be

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* Kresge 502 Cart: another hint that there is something genetic about prostate cancer is, we know that Osteo runs in families.

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* Kresge 502 Cart: men who have a brother or a father who has a diagnosis of prostate cancer have a 2 to 4 fold higher risk of prostate cancer themselves, and men with a mother or sister with breast cancer, breast cancer have a 1.5 to 1 point sevenfold higher risk of prostate cancer.

46:52

* Kresge 502 Cart: The other part piece of evidence comes from twin studies. So where twin studies

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* Kresge 502 Cart: study a monozygotic and dizygotic twins who share the environment in which they grow up in.

47:23

* Kresge 502 Cart: And they share all their genetics or share half of their genetics.

47:33

* Kresge 502 Cart: Okay?

47:40

* Kresge 502 Cart: And what we see from there is that plastic cancer melanoma isn't on the graph here, but plastic cancer and melanoma are the most heritable cancers due to genetic factors when we're partition into genetic factors and shared environment.

47:42

* Kresge 502 Cart: And the Y axis shows us something that we'll see in the next few slides is how much of that genetic risk can we already, with genetics from today explain this? Actually, the number has actually slightly increased since this slide. And I'll show you the latest numbers

48:03

* Kresge 502 Cart: when we talk about genetics. And we've heard a bit about this before we talk about rare variants and about common genetic variation. There's a lot of variation between our own genomes is where

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* Kresge 502 Cart: we're all different. At millions of sites in our in our genome

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* Kresge 502 Cart: for cancer risk, there are 2 things that are that are relevant.

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* Kresge 502 Cart: One is

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* Kresge 502 Cart: these rare but highly Pentrans mutations. So they have a strong effect on cancer risk.

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* Kresge 502 Cart: Those probably explain about 5 to 10% of cancer. So those are the Baraka one and 2 for breast ovarian and prostate cancer. So

48:59

* Kresge 502 Cart: they're rare. But when an individual has them. The risk is substantially elevated.

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* Kresge 502 Cart: and the second part is common genetic variation. So

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* Kresge 502 Cart: we all have common genetic variation, because that reference genome is not a real person

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* Kresge 502 Cart: on.

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* Kresge 502 Cart: and the effects of those common things that are slightly different between people. They're small individually, but when we sum them up over the entire genome. We can create scores that at the end of the day are actually quite useful for risk stratification, as I'll show you in a second.

49:33

* Kresge 502 Cart: These studies are genetic epidemiology studies. And I just wanted to show you how they look like this is the

49:52

* Kresge 502 Cart: second last big, genome, wide association study for for prostate cancer. It's a case control study. It's not the kind of case control study that you may learn in. And IP. 2, one. It's just cumulative incidence sampling like whoever has prostate cancer as a diagnosis is a case into.

50:00

* Kresge 502 Cart: and people of a certain age who don't. By then they're in control. And then these studies do logistic regression and adjust for age. And that's the analysis, basically. But it's huge numbers.

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* Kresge 502 Cart: And the other part, why, I'm showing you this study is, these studies are still to this day predominantly European ancestry, as you can see, based on the case and control counts compared to

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* Kresge 502 Cart: other continental origins.

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* Kresge 502 Cart: This is now the latest prostate cancer. Jiwaz. There are 451

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* Kresge 502 Cart: variants,

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* Kresge 502 Cart: single nucleotide polymorphisms or snps for prostate cancer risk that are statistically highly significant, some of them with a P value of 10 to the minus 600. So we're pretty sure that they're associated with prostate cancer from humongous sample sizes

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* Kresge 502 Cart: talk about in a second, how relevant actually, that 451 number is.

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* Kresge 502 Cart: And again, individually, the effects of each variant are very small, so that P value is really driven a lot by the fact that we have huge sample sizes.

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* Kresge 502 Cart: But when we then summarize those 451 variants in a single score. That's the Polygenic risk score. And this polygenic risk score you can

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* Kresge 502 Cart: what this study does here. It cuts it in half. It says, half of the population has a Prs below the medium, so 0 to percent, and the other half of the population has a Prs of 50 to to 100%.

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* Kresge 502 Cart: And what we can see is that the vast majority of prostate cancer is happening among people with polygenic risk score above the media. So 4 people who have a family history of prostate. So this is a combination here. So in fact, this low risk group here low risk. And no family history is about 40% of the population. And this other

51:59

* Kresge 502 Cart: group here is about 60%. So it's not really a higher risk group, because 60% of the population wouldn't necessarily qualify it higher as high risk. But what we can see here is there's at least 40% of the population that has a very, very low risk.

52:25

* Kresge 502 Cart: And this is for prostate cancer diagnosis and sort of to your point. A diagnosis is sort of would think comes before death. So people who don't get diagnoses of prostate cancer also don't

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* Kresge 502 Cart: die from us. So among people who don't have a cancer diagnosis, yet polygenic risk scores are very, very strong predictors, and they will probably be used clinically

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* Kresge 502 Cart: within the next few years, increasingly more, not just for prostate cancer. But as you saw in that graph that I showed you prostate cancer is is one of those examples where they perform the best. There are many common conditions where they don't perform as well as what we're seeing on this graph here, looking at the panel on the left.

53:08

* Kresge 502 Cart: I want you to think about the prevalence is that autopsy that you saw

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* Kresge 502 Cart: even in, say, ages 40, 50 years old? How how do those autopsy prevalences compare to these

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* Kresge 502 Cart: lifetime risks for prostate cancer, say, by age.

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* Kresge 502 Cart: 60 or 70.

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* Kresge 502 Cart: Thank you. What are you going to say? Something? No, no, that's great. It's interesting. Watching this talk and thinking like, oh, this is really interesting.

54:00

* Kresge 502 Cart: Do you remember what the prevalences were in the autopsy? Said, the percent of men who seem to have prostate cancer

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* Kresge 502 Cart: save in that age 40

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* Kresge 502 Cart: 16.

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* Kresge 502 Cart: What's that? Yes, about 30%. And so if you look at even at the group that had the highest polygenic score, the greatest genetic risk. What was their lifetime risk?

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* Kresge 502 Cart: Maybe

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* Kresge 502 Cart: maybe 8%

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* 2.

54:47

* Kresge 502 Cart: There's like of death. Yeah of death from prostate cancer. So yeah, so sort of to this point the majority of what could be diagnosed is not being diagnosed. And even this year is a very highly screened population. 80% of them actually got Psa tests.

54:48

* Kresge 502 Cart: Not an insignificant percent of those cases were

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* Kresge 502 Cart: bad policing scores. So it wasn't like they were just. oh, these really benign looking histologically cancers, but there was probably a third of them. I think, that were

55:16

* Kresge 502 Cart: higher degree tumors, which is super interesting. So why aren't they causing problems?

55:29

* Kresge 502 Cart: One thing about the pledging risk force that I want to emphasize is there are genetics there are in genes. There are lots of functional studies, but there's nothing

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* Kresge 502 Cart: magic about there being exactly that number. And like they're not necessarily cause. This is a prediction exercise. And this is from the previous Jiwas, which is the 269 Snps for prostate cancer. Now we're at 451.

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* Kresge 502 Cart: But what this is is fitting a model and looking at how many snps make the statistical significance threshold. And how good does the Auc get? And, as you can see, with the data that they had a few years ago the Aeoc didn't get better anymore. Once they added, more snps into the model. But it doesn't mean that these things here don't cause prostate cancer any longer.

56:09

* Kresge 502 Cart: It's just like it's a prediction exercise.

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* Kresge 502 Cart: So now.

56:39

* Kresge 502 Cart: I'd like to ask you a really tough question for that. You need your phones, or you can type in this number here on the bottom. So we've talked about from the twin studies that we know that 57% of prostate cancer risk is due to genetics. With that 95% confidence above 51 to 63.

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* Kresge 502 Cart: What do you think is the best interpretation of those data?

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* Kresge 502 Cart: So please do both. Because

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* Kresge 502 Cart: curious about your thoughts.

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* Kresge 502 Cart: Is it opening more good?

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* Kresge 502 Cart: I'll do, too, so I will get at least one wrong answer.

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* Kresge 502 Cart: Great! Keep going.

57:41

* Good distribution so far

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* Kresge 502 Cart: out of the 3 people. I can tell that there are more people with the phone hands.

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* Kresge 502 Cart: Not every epidemiologist can count. But I can't count that far.

58:02

* Kresge 502 Cart: so there don't feel like this is not an exam, so you don't need to be sure about what you're answering. Just pick one that sounds most reasonable to you.

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* But please do.

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* Kresge 502 Cart: You're all seeing the the distribution.

58:35

* Kresge 502 Cart: Hmm.

58:51

* thanks. Ok. A couple more, and now we're done. If you haven't voted yet, please do. And then we can give God.

58:56

* Kresge 502 Cart: Great. Okay, let's call it a day. So 69% of you thought that non-genetic factors are were difficult to explain. But they could explain up to 43% of prostate cancer risk.

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* And 25% of you said that genome, wide association studies

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* Kresge 502 Cart: of common genetic appearance will ultimately explain likely less than 57 genoc. The other 2 choices were not as popular.

59:33

* and

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* Kresge 502 Cart: I think you did just as well as

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* Kresge 502 Cart: when I showed the same exact, same answer to a group of urologists who've been studying prostate cancer for for many years. And

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* Kresge 502 Cart: so that's great to see.

1:00:04

* Kresge 502 Cart: I will still argue

1:00:07

* Kresge 502 Cart: that the right answer is actually this one.

1:00:09

* Kresge 502 Cart: And does anyone want to give the motivation for? Why you picked that answer and not the others, and I know this was a really hard question.

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* Kresge 502 Cart: and I fooled you with a condom in the bottom. I take the blame for that. and I changed my answer to this one.

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* Kresge 502 Cart: So

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* Kresge 502 Cart: it's the key word. Here is comedy rather than

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* Kresge 502 Cart: to your genetic variants, and it's getting back to identify yet high risk of dying from prostate cancer rather than

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* Kresge 502 Cart: having prostate cancer, but dying from other. That was what I thought when I changed my answer.

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* Kresge 502 Cart: there's a point that it says common genetic variants. So what I showed you a few slides ago is that 57% of prostate cancer risk to take the point. That interval is sort of the most likely estimate are due to genetics.

1:01:04

* Kresge 502 Cart: But there is common genetic variation, and then there is rare genetic variation. So it's likely that

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* Kresge 502 Cart: it's not all common genetic variation. So it's not all snips. But there is. There are things like Rocket, one, Brachit, 2, and so forth. And they're they're not rare there there as causes of cancer, 10% of cancers are probably caused by them. So

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* Kresge 502 Cart: that's why this is actually a thought. I'm giving you the right answer.

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* Kresge 502 Cart: At least, I thought.

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* Kresge 502 Cart: why is this one not the right answer? This is the one where it tricked you with a with a confidence.

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* and I'd love to walk you through.

1:02:04

* Kresge 502 Cart: But this goes back to the 1,900 thirtys to

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* big debate in

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* Kresge 502 Cart: actually the camp of the Eugenesis, who thought that humanity could be improved by basically killing people who looked

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* Kresge 502 Cart: genetically to be not the ones that we thought would be the most desirable, most healthy, and one of the leading statisticians run. Ronald Fisher, was their leading proponent from a statistics perspective to say, because

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* Kresge 502 Cart: this is the genetic contribution to disease. And this guy here Leslie Hawkman, was

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* Kresge 502 Cart: very vocal in in pointing out that we can't partition diseases as being genetic or non-genetic.

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* Kresge 502 Cart: and that has huge implications for what we do about them. For one, we shouldn't be killing people, of course, but we should be thinking about what we can do on

1:03:00

* Kresge 502 Cart: about the environment. So the genes and the environment don't sum up to 100%.

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* Kresge 502 Cart: So I fooled you by giving you, even though comfortable, with the same development that it seemed like you could subtract one from 100% and get the

1:03:18

* Kresge 502 Cart: every condition is always so. I don't know if it might be the sufficient component cause models. So I find them actually useful to to look at here.

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* Kresge 502 Cart: Each of them is one person who got on a disease, and maybe this is prostate cancer and made up some causes here for these 3 people in our population with 3 people and the Polygenic risk score is a component cause of all of them here it's a necessary cause, because in all of them. Maybe cosmic relation is, too. Nobody knows.

1:03:49

* Kresge 502 Cart: I don't know if cosmic radiation causes prostate cancer, you won't be able to say that's not the case because everybody's exposed, so we can't tell.

1:04:11

* Kresge 502 Cart: And then I put some, maybe more credible risk factors there, too. So while we make the counts here. we're seeing that an environmental risk factor. Cosmic variation is responsible for 100%. And Ips, a genetic factor is too.

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* Kresge 502 Cart: And we can even act on these. We could maybe eliminate cosmic radiation, which is nonsense.

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* Kresge 502 Cart: but that would get rid of all of it.

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* Kresge 502 Cart: or we could. And this is something that is being clinically done, we may have better interventions that people with a particular genetic condition benefit from this is what we do with Brca cures and breast cancer prevention, for example, mastectomies

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* Kresge 502 Cart: could think, well, maybe it's a prostatectomy need for it

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* Kresge 502 Cart: for prevention of prostate cancer. So there, we've altered, or we've acted upon knowledge of a genetic condition

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* Kresge 502 Cart: which has changed nothing about the contribution of the environment in that case of prostate cancer, because maybe this case wouldn't have occurred had this person been physically active.

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* Kresge 502 Cart: So to maybe bring these things together and really then get into what can we do about prostate cancer? We could think like, Oh, maybe the simplistic views here. The first one are germline respirants. They cause a prostate cancer diagnosis that we've got to treat it. Otherwise people die.

1:05:39

* Kresge 502 Cart: It's maybe not as that ignores a few things, and I think prevention from epidemiology perspective. We have more shots at cancer prevention. And one concept that we'll talk about is there's indolent. And there's aggressive prostate cancer. There are causes are different. Germline variants increase the risk of prostate cancer, but non genetic factors

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* Kresge 502 Cart: increase particularly the risk of aggressive prostate cancer. And then we can screen

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* Kresge 502 Cart: to reduce the stage of diagnosis. And then there are issues around treatment, access per and all of these things are relevant, not just for prevention in general, but particularly also for reducing racial disparities in in cancer, because

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* Kresge 502 Cart: otherwise the argument go as well among African Americans. It's all genetics. So all we can do is

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* Kresge 502 Cart: is increase access to treatment. But that would leave still a higher incidence. So it would still leave a higher disease growth.

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* Kresge 502 Cart: So what are those risk factors to talk about the first component here and those risk factors active along the life course. We've seen that cancer initiation is something that comes very early in life. We've seen among year olds that there is a lot of prostate cancer already. So we want to prevent that from happening. While that's

1:07:06

* Kresge 502 Cart: we'll probably need to think about things that act very early in life. But we also need to think about those cancers

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* Kresge 502 Cart: are clearly not relevant among year olds. Yet so there must be things that are happening during the remainder of the life course that make these cancers progress. Further, so that part is also important in genetic factors, or they act throughout life.

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* Kresge 502 Cart: So for total prostate cancer, which means a diagnosis of prostate cancer, regardless of what stage it is, what rate it is. These are what people would agree on as a risk factors. And that list is what people have a much easier time agreeing on

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* Kresge 502 Cart: here. African descent and genetic risk close Ir are separated. But

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* Kresge 502 Cart: that really we're talking about the same thing we're talking about when we're talking about genetics, and then height is

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* Kresge 502 Cart: a strong risk factor for prostate cancer. And actually, other cancers, too. So this is the meta analysis

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* Kresge 502 Cart: and height is actually interesting with regards to that life course that I just showed you. Because when do people get taught? While during puberty, so very early in life

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* Kresge 502 Cart: when both genetic and environmental

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* Kresge 502 Cart: conditions. So how much food is available, what kind of food, how much dairy do people consume? Those things do influence on bike gain, and they also influence.

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* Kresge 502 Cart: presumably the growth of the prostate. And we've seen that they influence the risk of prostitute.

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* Kresge 502 Cart: So all of this to suggest that this is one period during which risk factors are already acting on

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* Kresge 502 Cart: causing a cancer that will only become clinically apparent typically

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* Kresge 502 Cart: in people in their'. So an example of a very long lag time that concept that people have probably beaten into you already over the course of the time of this course, that in cancer epidemiology. There's often a long time between when somebody is exposed and when we see the effect of an exposure.

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* Kresge 502 Cart: So now let's imagine we would do a cancer epidemiology study, not of prostate cancer, but of every cancer down there like

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* Kresge 502 Cart: talking to, maybe not your grandparents, but your grandparents' grandparents, when they would be asking, what cancers did your parents die from? And they would be saying something like, Don't know exactly. Put something down there. That's sort of

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* Kresge 502 Cart: an example of misclassification. But it's the example of misclassification that you'll see we're doing in research still today. If we did that, if we threw them all into one bucket

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* Kresge 502 Cart: as risk factors. Out of that bucket would come age, race, and family history. Maybe we would get a few other risk factors because they're very, very strong risk. Factors

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* Kresge 502 Cart: come, maybe crip autism. So not understand the testicle for testicular cancer. Maybe each Pv has a very strong risk factor for a necessary factor for for cervical cancer

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* Kresge 502 Cart: may be obesity, because it's a very strong risk factor for kidney cancer from Demetrius cancer.

1:11:04

* Kresge 502 Cart: And we actually don't do throw all cancers into one bucket any longer for breast cancer. They're clinically used. Subtypes, molecular subtypes based on molecular tests done in tumor tissue. Those are clinically used because their therapy is attached to them, and from those we learn that

1:11:12

* Kresge 502 Cart: being pregnant more often decreases the risk of basically hormone receptor, positive breast cancers. but increases the risk of triple negative breast cancer.

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* Kresge 502 Cart: And if we throw all breast cancer into one bucket. we put Cnola Association.

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* Kresge 502 Cart: Oh. we still throw mostly prostate cancer all into one bucket, and that is one of the explanations why the list of risk factors that people can universally agree on

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* Kresge 502 Cart: is shorter than for for other cancers, so which in turn also means there's a lot of good epidemiology that we can still do by

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* Kresge 502 Cart: by getting beyond our

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* Kresge 502 Cart: growing things together that don't belong together. So we're not

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* Kresge 502 Cart: getting at least agreement out of that bucket again. So this is the list of risk factors for advanced or fatal prostate cancer. So those are prostate cancers that are no longer confined to the prostate cancer that people die from. And all of a sudden that list gets a lot longer, because if you keep searching for risk factors for

1:12:21

* Kresge 502 Cart: total plastic cancer, those are cancers, while everything is confounded by Psa screening, because people get screened for cancer when they're interested in health maintenance. People who are interested in health maintenance

1:12:44

* Kresge 502 Cart: are healthier and psa screening detects certain types of prostate cancers better than others.

1:12:57

* Kresge 502 Cart: But when we talk about cancers that have the potential to metastasize the potential to cause death, then that is a different subset, and these are

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* Kresge 502 Cart: possible or probable risk factors.

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* Kresge 502 Cart: I'd like to show you one example of physical activity and prostate cancer.

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* Kresge 502 Cart: Now, here, we're not looking at the outcome separately by whether the cancer has metastasized or not.

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* Kresge 502 Cart: We're looking at malikar subtypes of prostate cancers because they exist in prostate cancer just like they exist in other cancers and other cancers. I just mentioned asteroid receptor or hormone receptors that is, in breast cancer.

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* Kresge 502 Cart: in colon cancer, microsatellite instability, each Pv positive added neck cancer. So those are the common clinically used subtypes. Again, because there are therapies attached to them. That's why there's also a lot of studies, because everyone who has a diagnosis of these cancers. That information is on the medical record for prostate cancer. There's no information about subtypes on the medical record right now.

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* Kresge 502 Cart: but there are molecular subtypes. And indeed, the gene fusion between 2 genes er g and tempus 2

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* Kresge 502 Cart: is about present in what half of all prostate cancer. So it's not like a necessary thing to study, and as you can see here, across quintiles of vigorous physical activity.

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* Kresge 502 Cart: the association with urb negative prostate cancers is completely null versus. There is at least the suggestion of a protective association among erg positive prostate cancer.

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* Kresge 502 Cart: Now we see similar things to go back to the earlier classification for advanced and lethal, so advanced increased stage lethal meaning metastases or prostate cancer death. Again, that's where

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* Kresge 502 Cart: associations between protective

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* Kresge 502 Cart: factors and risk factors and those prostate cancer outcomes are even detectable.

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* Kresge 502 Cart: Interestingly, for these results, the results are even stronger among men who were all undergoing Psp screening.

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* Kresge 502 Cart: Why is that that important? I would particularly want to look among highly grief men as opposed to just everyone

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* intend to be wild.

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* Kresge 502 Cart: Yep. And why? How would that influence the results of the study

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* Kresge 502 Cart: I was working. If you have. is that what you're asking how to effect the testimony, or what were the results here? Yeah, yeah, I think you would under estimate.

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* Yeah.

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* Kresge 502 Cart: Because the

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* Kresge 502 Cart: in Egypt.

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* Kresge 502 Cart: you know, protected behaviors like they would like to

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* reduce the risk.

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* Kresge 502 Cart: Yeah. So it's an example of confounding exactly as you're as you're describing. So more physical activity goes along with more Psa tests so leading to

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* Kresge 502 Cart: diagnosis of cancer that otherwise would have not been diagnosed, but

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* Kresge 502 Cart: The causal effect of

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* Kresge 502 Cart: maybe preventing prostate cancer could be masked by that. So that's one part of why. And it's a very important part that's confounding the other part is probably something around effect modification, that if you screen at regular intervals you're more likely to pick up a cancer that has been sitting there all alone.

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* Kresge 502 Cart: So it it peaks up cancers that are slower to grow, and are. and are more more indolent as opposed. So you can imagine when you do a screening test. Maybe every other year cancers that grow very quickly

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* Kresge 502 Cart: may become clinically apparent between those 2 on the screening of faces. So that's for length time.

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* Kresge 502 Cart: So for

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* Kresge 502 Cart: so the other part about lifestyle, we just quickly talked about on physical activity. But of course there's other modifiable risk factors. Now the big question is, I've argued with you that

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* Kresge 502 Cart: genetics and environment are not mutually exclusive. But what about people who have bad genetics meaning. There are higher risk because of genetics. Is

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* Kresge 502 Cart: is there cancer risk still amenable to prevention? So to walk you through here? This is a study again, stratifying people by their polygenic risk score. And again, as I've shown you before, the polygenic risk scores work really well.

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* Kresge 502 Cart: the lifetime risk of any prostate cancer type is something about 15% and goes up to 50% among people in the highest quartile and the same for metastases. So death, comprising cancer or substantial differences by genetic predisposition, just common genetic variants developed.

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* Kresge 502 Cart: So I said, this is one example of a healthy lifestyle score, so very.

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* Kresge 502 Cart: very basic things in a way very leniently defined.

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* Kresge 502 Cart: And now we're stratifying people into 12 different groups, essentially, people with very low, genetic risk, and people with quite high genetic risk, and some intermediate cancers. So maybe let's look at the extremes because they're most telling. There's very little prostate cancer among people with low genetic risk. So there's

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* Kresge 502 Cart: hard to say much.

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* Kresge 502 Cart: So that's an example of good risk. And there's a lot of prostate cancer. Now, we're looking at prostate cancer

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* Kresge 502 Cart: metastases and death here among people with a high genetic risk.

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* Kresge 502 Cart: However, when you then stratify people by lifestyle among people with higher genetic risk.

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* Kresge 502 Cart: you see that

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* Kresge 502 Cart: people with a healthy lifestyle have substantially delayed an onset of metastatic and fatal plastic cancer at much lower rates and lower lifetime rates. Whatever measure you want to know

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* Kresge 502 Cart: other

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* Kresge 502 Cart: you have concerns about what could be going on there.

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* Kresge 502 Cart: Could it be that people are genetically different, and they have a different lifestyle or something?

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* Kresge 502 Cart: Gotcha

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* Kresge 502 Cart: turns out. No, I'm first.

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* Kresge 502 Cart: We've done these studies for for a while. Now we can't make this go away and like it's been seen in other studies, too. This is not a result just for prostate cancer. This is something that we keep seeing over and over for different types of cancers, but also for genetic predisposition to other chronic, chronic, common chronic conditions. People at a high genetic risk

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* Kresge 502 Cart: are just as amenable to, or might benefit in relative terms just as much as people with low genetic risk. But in absolute terms, as you can clearly see from these primitive incidents, curves, their benefit is even much higher, because there's more happening.

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* Kresge 502 Cart: Ok, let's talk about screening as another means. And we've covered a lot of ground on screening already

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* Kresge 502 Cart: with meth. I've just not talked much about what Psa actually is. Psa is just a biomarker. It's a protein that's made by prostate. It's not made by prostate cancer necessary. It's made by B prostate. And that explains why it's not the perfect test.

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* Kresge 502 Cart: And it's often thought to be

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* Kresge 502 Cart: just a marker of prostate cancer. And initially, it was actually meant to be a marker just for measuring progression of prostate cancer, but was quickly repurposed for screening, for prostate cancer, which is, as you can imagine, a much bigger market.

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* Kresge 502 Cart: and there's

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* Kresge 502 Cart: it gets binderized. And when it reaches a certain level, then it typically triggers a biopsy of the prostate. Nowadays, also an MRI of the prostate.

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* Kresge 502 Cart: So what pse does is it buys us leap time and lead. Time means there are these 7 to 10 years between when there is prostate cancer that is easily tactical by Psa screening. And the time this cancer would be clinically diagnosed otherwise.

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* Kresge 502 Cart: And if we did the blood test, it shifts the diagnosis. Those 7 to 10 years work. So the effect of the screening is to make use of that lead time. So there's lead time bias. But screening actually buys us that lead time. And it's those 7 to 10 years during which

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* Kresge 502 Cart: screening can be beneficial. If there is a treatment that works better now as if we had waited those 7 to 10 years, and that's more important. But nobody should get screened if they don't have access to treatment, because then we're only harmed.

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* Kresge 502 Cart: There's been a lot of talk about whether prostate cancer screening works, and particularly in the United States, because the American trial showed that it didn't work.

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* Kresge 502 Cart: But it turned out over the years that actually the American trial had not worked because it was meant to compare Psa screening versus, not psa screening. It turned out

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* Kresge 502 Cart: that the intention to treat the analysis of that trial was completely misleading, because the people in the control arm had also gotten Psa script. So it was comparing a lot of screening to even more psa screening and even more psa screening was not beneficial.

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* Kresge 502 Cart: There was a European trial that did not have the same issue.

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* Kresge 502 Cart: And this trial has shown that Psa screening reduces

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* Kresge 502 Cart: the risk offered

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* Kresge 502 Cart: death from passive cancer by about 20%. So relative risk of point heat which translates into this risk difference of 0 point 1 injected at 16 liters.

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* Kresge 502 Cart: and the numbers needed to invite and to diagnose or higher.

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* Kresge 502 Cart: get them at first, but they're actually very similar to breast cancer. This is how mammography screening looks like, too. This is how many people do you need to invite. And this is then the number of people who need to be treated in order to prevent one death

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* Kresge 502 Cart: from this specific cost. So we actually discussed a recent article by Welch and Day in class together, which is really interesting in terms of thinking about swimming trials.

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* Kresge 502 Cart: cancer, specific death, etc. So very timely discussion. As you can see, this is a small contribution to all death, so it's hard, with this intervention to make it dent into death from any cause.

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* Kresge 502 Cart: but it works for prostate cancer and keep in mind. The absolute risk may be very different in a group at very high, absolute risk, to begin with. So no very high absolute risk to begin with, or risk ratio of 0 point 8 or a risk ratio of 0 point 8 actually may make a difference.

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* Kresge 502 Cart: but it may.

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* Kresge 502 Cart: For people who are low risk. To begin with, it may not be a good.

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* Kresge 502 Cart: What's the incidence?

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* Kresge 502 Cart: Greater issue for plastic cancer in the European trial. So in the trial that worked, comparing screening versus no screening. would you think it's 1.6 0 point 8 or

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* Kresge 502 Cart: completely null

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* Kresge 502 Cart: who votes for 8?

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* Kresge 502 Cart: One vote for A, who votes for B. You don't need to know. But what will you guess? I don't expect you to know

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* Kresge 502 Cart: on gas for a P. And he asks for a seat.

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* Kresge 502 Cart: We want to do a again. Yes, great. I love it so. Yes, screening detects cancer. So screening does detect more cancer. So that's exactly what we've seen. When we looked at the trends over time, that hump in prostate cancer incidence. That was Psa screening. That's exactly the effect of of what it does. It's not a colonoscopy where you move a precursor.

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* Kresge 502 Cart: And incidence actually goes, though, this is a test that detects cancer. So it makes incidence go up.

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* Kresge 502 Cart: Similarly, cervical cancer is another example, right?

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* Kresge 502 Cart: And because of these issues around, does it work? Does it not work

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* Kresge 502 Cart: you as preventive sources. Task force has been going back and forth about whether screening is recommended. And that's why you see these changes in incidents over time. And of course there are concerns about when you don't screen

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* Kresge 502 Cart: those decreases in prostate cancer mortality that we've been seeing now for a long time may not be continuum.

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* Kresge 502 Cart: I may be plateauing, but at the same time

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* Kresge 502 Cart: the sensitivity of the screening approach, so

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* Kresge 502 Cart: that Psa test, plus everything else that you do so, the screening program still needs to be better than what we're doing today, because, frankly, it is still driven by incentives that incentivize diagnosing and triggering more cases, despite everything that has been done

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* Kresge 502 Cart: so. And

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* Kresge 502 Cart: this is the effect that we're seeing on on survival. This relative survival is where we where we started.

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* Kresge 502 Cart: we started with relative survival of prostate cancer in the 1,900 seventys around 70 to

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* Kresge 502 Cart: 70%, just about where breast cancer was. And now it's at 99%. So it's a lot of progress.

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* Kresge 502 Cart: But it's both improvement in treatment because of screening. But it is also diagnosing lots of people who would not necessarily need to be undiagnosed.

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* Kresge 502 Cart: So with that, I'd like to and

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* Kresge 502 Cart: and summarize that prostate cancer is a major public health burden with strong racial disparities both for incidence and mortality, and those racial disparities are both, and always at the same time, due to genetics as well as to non genetic factors.

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* Kresge 502 Cart: Puberty is a critical period for exposures that affect prostate cancer. But then, of course.

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* Kresge 502 Cart: risk factors along the life course have an effect on to

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* Kresge 502 Cart: the risk. Factors for prostate cancer are a lot more controversial. This is a cancer that really still needs a lot of work. You can't do this case control study with a couple 100 people. Ask them, are you a smoker? And you've got 90% of your population as a fraction right there, as people did in the for lung cancer. This is really a cancer that is a lot harder to

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* Kresge 502 Cart: to study, but also a lot more interesting. I personally. Thank you. Please.

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* Kresge 502 Cart: those risk factors are really for advanced prostate cancer, the ones on this one pattern that I didn't mention for the risk factors that we've seen insulin and growth factors.

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* Kresge 502 Cart: both during puberty as well as for the other risk. Factors during the life course have a big impact. And we talked about Psea screening. It reduces on prostate cancer mortality and really profoundly impacts

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* Kresge 502 Cart: the observed burden of prostate cancer. And it is.

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* Kresge 502 Cart: as always, we've looked at prostate cancer very early in life, that it is a disease of older men. So that is.

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* Kresge 502 Cart: that is important in all considerations. Raw treatment. Great. Thank you. We're at the hour

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* here for questions.

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* Kresge 502 Cart: I know we're a little over time. So I was saying, maybe if we don't have other questions specifically, you'll be here. And you also have Dr. Stubbs email address as well, exciting projects for people looking for a research project.