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

0:08

* 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

0:35

* 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

1:14

* 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.

1:42

* 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

1:51

* 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?

2:06

* I think.

2:24

* Hello!

2:43

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

2:53

* 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,

2:58

* 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

3:19

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

3:36

* Kresge 502 Cart: Okay? So it looks like

3:38

* 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

3:42

* 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.

4:07

* 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

4:22

* 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.

4:56

* 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

5:47

* 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.

6:30

* 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.

6:36

* 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.

6:59

* 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

7:22

* 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

8:22

* 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

8:31

* 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.

9:03

* 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.

9:13

* 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.

10:00

* 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

10:15

* 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

11:04

* 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

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* 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

24:02

* 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.

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* 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.

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* 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.

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* 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

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* 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.

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* 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.

40:11

* 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.

40:43

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

41:05

* 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.

41:36

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

41:53

* 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

42:24

* 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.

42:27

* 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

42:41

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

43:09

* 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.

43:16

* 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.

43:38

* 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

43:54

* 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.

44:20

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

44:29

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

44:39

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

44:46

* Kresge 502 Cart: Sorry.

44:57

* 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.

45:24

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

45:49

* 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

45:55

* 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.

46:20

* 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.

46:34

* 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

47:02

* 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.

47:10

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

47:34

* 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

47:55

* 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

48:19

* 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

48:49

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

49:15

* 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?

49:48

* Kresge 502 Cart: Okay? So I think

50:01

* 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.

50:05

* 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

50:19

* 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.

50:41

* 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

50:59

* 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.

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* 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

54:04

* 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

55:08

* 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.

55:49

* 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

56:29

* 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

59:02

* 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

59:04

* 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

1:00:00

* 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.

1:01:12

* 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.

1:01:23

* 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

1:01:55

* 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

1:03:04

* 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

1:11:53

* 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

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* 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.

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* Kresge 502 Cart: Okay, that's probably the last point I'll make this is.

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* Kresge 502 Cart: it's a similar point, but maybe a little bit different

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* 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

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* Kresge 502 Cart: and beta carotene

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* 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

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* Kresge 502 Cart: vitamin a and vitamin e they're antioxidants.

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* 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.

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* 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.

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* 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.

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* 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

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* 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.

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* Kresge 502 Cart: And you know, within like 5 feet, 6 years, like 4% have lung cancer, that's extremely high.

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* 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.

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* Kresge 502 Cart: Alfred teferall didn't work prevent lyme cancer. This truck Beta charity

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* Kresge 502 Cart: like, okay, Betty Carotene, you know you get that Beta Carotene and carrots are high in Beta Carotene right?

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* 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

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* 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.

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* Kresge 502 Cart: not only is Beta Carotene like, not beneficial. It's not even neutral. It's actually bad fuel. So

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* 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.

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* 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

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* 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.

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* 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.

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* 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.

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* 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

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* Kresge 502 Cart: summarizes like his, like kind of my take on that Atpc trial. So.

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* 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.

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* 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.

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* 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,

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* 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

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* Kresge 502 Cart: like

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* 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.

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* 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

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* 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?

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* Kresge 502 Cart: Sorry. I think we're 2 min over. So

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* Kresge 502 Cart: there are any questions II mean, feel free to leave, but happy to have questions, otherwise we'll continue Thursday.