* Kresge 502 Cart: Stop, stop prosecutor

0:15

* technology. Conrad is a physician, scientist trained in internal medicine, received his mph here at the Harvard School of Public Health, and has been engaged in really very innovative research across the pathogenesis and cancer continuum and prostate cancer.

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* and has given this lecture in our class. Now, this is your third year doing it, and really excited that he's come back. He's an assistant professor, both at Harvard Medical School and here at the Harvard school of Public health. So, however, thank you so much. We're delighted to have you have your lecture today. Thank you, Lorelei, and welcome everyone. If you've ever been to Rome, not the Rome in Italy, but Rome with the Vatican, and lecture to the Pope

1:04

* Kresge 502 Cart: about cat cynicism. That's how I feel when I lectured to these 2. So I'd love to talk with you today about 3 fundamental things of prostate cancer. That's the first 3 things on this slide here, and that is some clinical features.

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* Kresge 502 Cart: what is prostate cancer? And then we'll talk about the descriptive epidemiology. How much of prostate cancer is there, and particularly racial disparities in prostate cancer. We'll talk about inherited genetic factors, which are a big contributor.

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* Kresge 502 Cart: And then, in the second part, if you will, are the things that talk about, what can we do about this? And the first one is risk factors and primary prevention. The second part is around screening Psa screening, and that we always need to think about Psa screening when we talk about prostate cancer. And then the last part will briefly talk about

2:13

* Kresge 502 Cart: cancer, survivorship and cancer survival and treatment as an important contributor to the burden of prostate cancer and to the burden that men with prostate cancer face. I would like you to interrupt me

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* Kresge 502 Cart: at any point. I will ask you questions if you don't ask me. But please please still jump in right away. So let's talk about what prostate cancer is what is the prostate? The prostate is probably the most boring organ in the human body, and I mean this, after studying this organ or

2:50

* Kresge 502 Cart: for 10 years. So it's hidden in the pelvis. It's so unimportant that half of humanity can very well, and maybe even better, do without it. So

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* Kresge 502 Cart: it's next to the bladder next to the rectum, and not a very interesting spot of the human body, and we would not be talking about this organ ever, almost ever in medicine if it wasn't the site for cancer. And one of the most common cancers in

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* and

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* Kresge 502 Cart: in people. So that's really the most important thing about cancer

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* Kresge 502 Cart: is. But the prostate is cancer. There's basically 2 other reasonably common conditions about the prostate that ever come to to light. As the prostate grows with age. So it's

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* Kresge 502 Cart: not uncommon reason for people not able to pee, because the urethra goes directly through the prostate and the other condition there is is prostateis, but other than that, it's

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* Kresge 502 Cart: such a common place for cancer to originate.

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* Kresge 502 Cart: But, we talk about prostate cancer. There are 2 dimensions that are important when we talk about it. One is.

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* Kresge 502 Cart: how big is the cancer and how much is there? So that's staging? That's similar to what you see in in other solid tumors. And we'll also talk about grade. Which basically means, how does the tumor look like under the microscope? So for staging, we're talking about 3 different

4:42

* Kresge 502 Cart: facets of of stage. The first one is the tea stage. So that talks about the primary tumor. So there we're talking about this walnut sized organ that the prostate is, and

5:02

* Kresge 502 Cart: T. 3, and which isn't depicted here, basically say, how big is that cancer within the prostate, or how much has it already grown slightly beyond the prostate. So a would, for example, be invading the bladder, which is an organ that's sitting right next to the prostate.

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* Kresge 502 Cart: So here we're really talking about cancer in the prostate. The big difference is whether or not cancer has spread to distant organs. As with other solid tumors, so the other components of Tnm staging is whether that termer has spread to lymph nodes.

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* Kresge 502 Cart: This is

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* Kresge 502 Cart: more challenging to talk about and not as important as the third part of Tmm's brain staging, which is distant Midhouse disease. So

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* Kresge 502 Cart: other parts of the body, being affected by metastases of prostate cancer, are the most common site

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* Kresge 502 Cart: of metastasis

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* Kresge 502 Cart: from prostate cancer is bone. So there are basically 2 common clinical presentations of prostate cancer, or 3. The first and most common one is

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* Kresge 502 Cart: no symptoms at all, and the cancer is detected by Psa screening. And that's why we'll need to speak about Psa screening for sure

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* Kresge 502 Cart: other than through a lens of prevention. The second one is, you can imagine this tumor growing and pressing on the Urethbrasine, and the third, which is a sign of distant metastases, is the tumor already having spread beyond the prostate, and those

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* Kresge 502 Cart: those presentations are really due to pain and commonly back pain. So the classical presentation is

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* Kresge 502 Cart: elderly men coming to an emergency room with trouble, peeing, and back pain, who hasn't seen primary care for a few humors, and that would then be metastatic, prostate sort of as the classical vignette to picture a person for you.

7:12

* Kresge 502 Cart: But again, the majority of cases, at least in the United States nowadays, are of T stage onec. Not metastatic, that are detected by Psd. Springs, so by blood tests only, and are not even culpable on the organ. Why is staging so important? If we look at relative survival

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* Kresge 502 Cart: in the

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* Kresge 502 Cart: in 5 years after diagnosis for those 70% of patients diagnosed with localized prostate cancer and smashing proportion with regional prostate cancer. So nodal positive lymph nodes, the relative survival is

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* Kresge 502 Cart: close to 100%, or it can actually be greater than 100%. Does everybody remember when Michelle and Colleen talked about different measures of survival, what relative survival is, and how it's different from, say, just looking at survival as a concept. Do you remember what relative survival is? Exactly, and why it could be greater than 100%

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* Kresge 502 Cart: sorry to interrupt. But

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* Kresge 502 Cart: it's weird right. Why would survival be greater than 100%. It can only live once, I guess.

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* What are they doing in relative survival and calculating? What are they comparing

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* Kresge 502 Cart: survival, too, that it could be bigger than 100%.

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* Kresge 502 Cart: I see some of you wanting to say something. Yeah.

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* Kresge 502 Cart: that's a free individual. because of some people screamed out.

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* so that's why I did.

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* Kresge 502 Cart: Yeah, great. I'll just repeat what both said. So basically, relative survival is a comparison to people typically of the same age and in sex, or what the cancer registry or courts

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* Kresge 502 Cart: over the 5 years. So it really depends on who is diagnosed with cancer. So it's comparing to

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* Kresge 502 Cart: to basically people at the same age. And so that means, if people who get a diagnosis of prostate cancer are more healthy.

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* Kresge 502 Cart: the relative survival will be better, even though they have cancer. And we'll talk about these are cancers, localized prostate cancers. They tend to be very indolent. So it's really about

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* Kresge 502 Cart: different people getting getting diagnosed.

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* Kresge 502 Cart: but not to forget. And we'll see this in just a bit. The survival of metastatic prostate cancer

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* Kresge 502 Cart: is poor and continues to be poor, and

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* Kresge 502 Cart: there is no curative therapy for metastatic prostate cancer and metastatic prostate. Cancer is a big public health burden. So this is one of the fundamental challenges that we face with this cancer is

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* Kresge 502 Cart: that

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* Kresge 502 Cart: relative survival of people with localized prostate cancer is very, very high, but it is still bad for people with metastatic prostate cancer.

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* Kresge 502 Cart: So I promise there is a different second aspect to sort of one of the 2 big perspectives on prostate cancer. And that is grade. This is a slide that's really for your reference. Nobody will ask you about how you define Gleason grade and score.

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* Kresge 502 Cart: but it basically is on a visual description on how the tissue looks like under a microscope and typically prostate tissue looks organized. It's a gland that has a function. This organ that is so boring does have a function, it produces

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* Kresge 502 Cart: a fluid that helps with sperm. And but that is really

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* Kresge 502 Cart: the organizing pattern of this tissue is really very clear, and as cancer progresses or as cancer initiates and then progresses through its grades, the tissue becomes increasingly disorganized.

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* Kresge 502 Cart: So that's what visually this system is is capturing nowadays, we would be creating an AI algorithm that looks at the tissue and then picks up what is bad about it. This patterning was actually created by a pathologist, looking at

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* Kresge 502 Cart: many cases and sort of deciding visually. Oh, these ones look bad, and these ones don't look bad, and he gave them numbers, and his name was nieces, and that's why Lesen's words from the and and is held up, and is actually an even stronger predictor of prognosis and prostate cancer than stages, or, you see in that stages

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* Kresge 502 Cart: is a strong predictor.

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* Kresge 502 Cart: So now I have a lot of questions for you, one big one very important graph to to look at, and I'm curious about your thoughts. What you make out of these numbers that I'm showing you here. What I'm showing you here are is the prevalence of prostate cancer at autopsy.

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* Kresge 502 Cart: of men who died from other reasons than prostate cancer.

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* Kresge 502 Cart: So I lost

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* Kresge 502 Cart: because the numbers are smaller, give use it. So the scale here goes from 0 to 60%.

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* Kresge 502 Cart: And these are the 3 bars are for different racial categorizations.

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* Kresge 502 Cart: What do you make out of this data. And what do they tell you about prostate cancer? I'm curious about your thoughts. There's so much that we can read into this

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* Kresge 502 Cart: right? So again, none of these people had a diagnosis of prostate cancer. Exactly. So that is important. Thank you, Laura. So these people did not have a diagnosis of prostate cancer in life. They died from car accidents, they died from heart attacks, they died from anything but prostate cancer, and then they had an autopsy, and I'll just look at their prostate tissue and decided whether or not there was histologically tumor present in in that.

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* Kresge 502 Cart: Yes, significant in the US. White European populations between 29 to 30 to 39. Which is interesting.

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* Yeah.

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* Kresge 502 Cart: Great observation. Why do you think that is, or what could be done out there? I would assume. It's just

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* chain also

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* Kresge 502 Cart: issue.

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* Kresge 502 Cart: Yeah, I mean, that's very hard to know from these graphs. This is one of the most important points, the prevalence of toxic cancer at autopsy already goes up to very high levels

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* Kresge 502 Cart: for 30 to 39 year olds. So a lot of us

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* Kresge 502 Cart: quarter to a third is the prevalence in an age group where basically nobody gets diagnosed clinically with plastic cancer.

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* Kresge 502 Cart: Yes, so I can tell with you from the regardless of race.

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* Kresge 502 Cart: And they erased themselves, having prostate cancer.

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* Kresge 502 Cart: basically age.

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* Kresge 502 Cart: And, second, that African-americans tend to have a larger percentage of prostate cancer.

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* Kresge 502 Cart: not offering the treatment or the screening tools in that population. That's why they are having

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* Kresge 502 Cart: diagnosis. Yes, so great. 2 very important observations. One is, I'm

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* Kresge 502 Cart: there is a strong age relationship. The first part is exactly what your classmates already said. Already, at a very young age the prevalence is very high, but then there's a strong increase with age in addition to that, and then you point it to

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* Kresge 502 Cart: differences between these race calculation that we often use

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* Kresge 502 Cart: on. And one explanation could be, there's

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* Kresge 502 Cart: we're sort of in us white and European patients. Here, we're sort of selecting away the cases versus in the black group here who haven't diagnosed them in life. So that's an interesting question.

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* Kresge 502 Cart: yeah, what do you think? What could? What could be going on there?

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* I mean, it could just be that.

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* Kresge 502 Cart: And then.

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* Kresge 502 Cart: second, maybe we are maintenance

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* Kresge 502 Cart: right on.

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* Yeah. So those are 2 important contributors. I like that. You're starting with the first. Yes, life expectancy is a lot shorter

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* Kresge 502 Cart: in black men in the United States. So that's one part of the explanation. The other one is, there were just fewer studies also. So the data weren't sufficient to come up with reasonably

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* Kresge 502 Cart: precise estimates for that group. But

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* Kresge 502 Cart: prostate cancer. To make one thing clear, prostate cancer does not disappear over age of 80. That's definitely not the message of this slide, and it's also not that they've all died from prostate cancer.

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* Kresge 502 Cart: Other thoughts about this graph

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* Kresge 502 Cart: great points that will be

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* Kresge 502 Cart: talking about.

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* Kresge 502 Cart: I'll show you one other annotation here. Yes, great.

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* Kresge 502 Cart: Hmm.

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* Kresge 502 Cart: oh, yeah, yeah. Great moment. Yeah. So this is a, this is actually a meta-analysis. So this isn't. This isn't just one single original study that I pick because it is really a pooling of

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* Kresge 502 Cart: Already the available autopsy studies that were available up until, like 10 years ago, there might be a few additional ones. I know there's one being done now. But yeah, racial categories are always

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* Kresge 502 Cart: question and yes, leaving out on other groups if more so

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* Kresge 502 Cart: great. So the other part annotation that I wanted to give here is on the lifetime, risk and lifetime.

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* Kresge 502 Cart: The left side of this slide shows you what we could find if we auto seed everyone, we're not doing that.

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* Kresge 502 Cart: So of these huge prevalence numbers here the majority will remain undiagnosed.

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* Kresge 502 Cart: And what I'm showing you on the right here with that 13% lifetime risk is this is the cumulative incidence over a lifetime of being diagnosed with prostate cancer.

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* Kresge 502 Cart: So the big take home message, here is there is way, more plastic cancer that could be diagnosed than what we are, even currently with very intensive screening diagnosed.

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* Kresge 502 Cart: and we'll come back to whether that is good or bad. So let's focus a little bit more on how prostate cancer looks like in living people, because at the end of the day that's a little bit more important for public health than what we could be labeling people with.

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* And I'd like to show you

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* Kresge 502 Cart: interesting overview of the global burden of

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* Kresge 502 Cart: prostate cancer. This is prostate cancer incidence. So this is new diagnoses. There are 1.4 million. About incident, prostate cancers globally.

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* Kresge 502 Cart: with very strong differences

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* Kresge 502 Cart: by both our continent and by a country with particularly notable. Lower incidence rates in Asia. I think that's the most important pattern to to point out here.

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* Kresge 502 Cart: And then for prostate cancer mortality a different.

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* Kresge 502 Cart: broader picture, with particularly notable high mortality rates

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* Kresge 502 Cart: in sub Saharan Africa and in the Caribbean. and again.

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* Kresge 502 Cart: relatively low mortality rates in Asia.

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* and when we look at different.

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* Kresge 502 Cart: a slightly subcontinental level breakdown. We see that prostate cancer, incidence and mortality

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* Kresge 502 Cart: don't for one, differ dramatically between different regions, and that they, as you can see don't track very well with each other.

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* Kresge 502 Cart: and what we'll be seeing. Why, why, that might be. Let's look at the United States for a bit.

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* Kresge 502 Cart: So these are the prostate cancer incidence trends in the United States. And here we're down to 2 racial groups with an combination of

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* Kresge 502 Cart: ignoring Hispanic ethnicity.

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* Kresge 502 Cart: or some what could be going on for these 2 graphs over time. What is happening there?

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* Kresge 502 Cart: That's a badwa. But we're seeing there.

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* Kresge 502 Cart: Yes.

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* heard in Sweden.

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* Then it's possible.

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* Kresge 502 Cart: Yes, great. So what we're seeing the big

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* Kresge 502 Cart: thing here is, we see a jump in the incidence. So in the number of diagnosed cases every year in both racial groups, slightly differently. When Psea screening came around in the early. And we'll talk more about what screening, how that entered.

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* Kresge 502 Cart: What's what could be going on here in more recent years?

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* Kresge 502 Cart: Any idea?

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* Kresge 502 Cart: Yep, maybe you're more valid test. So that's also true.

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* Kresge 502 Cart: Yeah, that would.

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* Kresge 502 Cart: That is something that people are working on.

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* Kresge 502 Cart: Unfortunately, it's not quite what we're seeing, what we're seeing here yet. We hope to see better, smarter testing in the next few years. The Psa test

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* Kresge 502 Cart: so far. To mention the Psea test will remain part of the mix. So the Psa test is actually not a bad test, but it's not been used very smartly. But what people are doing exactly to your point is, they're integrating information from additional tests, from genetic tests, from imaging tests such as Mris.

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* Kresge 502 Cart: or they diagnose people with prostate cancer, with the idea being to avoid diagnoses of

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* Kresge 502 Cart: of cancers that don't need to be diagnosed and

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* Kresge 502 Cart: and diagnosing people who do need a diagnosis or would benefit from a diagnosis because they would benefit from treatment in order to avoid that risk of progression to metastatic prostate cancer that has such a high risk of of death. So what you're seeing here is actually changes in clinical practice guidelines here

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* Kresge 502 Cart: around 2,009 on the US. Preventative services task force. That is not the only body that makes cancer screening guidelines, but it's the body that makes cancer screening guidelines that affect reimbursement. They came out with a recommendation against prostate cancer screening. So what you see here is just less screening.

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* Kresge 502 Cart: And in 2015

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* Kresge 502 Cart: they changed course and recommended prostate cancer screening again. So then, you see incidents going up again.

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* Kresge 502 Cart: So those are really the major. Of course there's more going on here, but those are the major factors in fluids.

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* Kresge 502 Cart: These were mortality trends. What do you think is going on there?

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* Kresge 502 Cart: Yes.

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* Kresge 502 Cart: musical

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* 2,000.

26:02

* Kresge 502 Cart: And then I guess metal truth.

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* Kresge 502 Cart: Umhm, so that so the first part is very interesting. Basically, it means, yes, there is screening here. And that leads to more people getting a label of prostate cancer and having a chance to die from it. But at the same time it also meant that

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* Kresge 502 Cart: more, that we started diagnosing and treating people whose cancers would have later progressed to metastatic prostate cancer. And they would have died from that. So what we're seeing this continued decline ever since is actually an effect of Psa screening. So we're seeing the benefit of Psa screening in these decreasing rates here.

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* Kresge 502 Cart: Anything else? That's apparent. Very

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* maybe jumping at you when we look at the 2 curves.

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* Kresge 502 Cart: others on. There's the stark difference between the black and the curve for black and for for white men here for the United States, and we see that the uptake of that the changes weren't as dramatic in the in the lower.

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* Kresge 502 Cart: And

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* Kresge 502 Cart: we're we're more notable in in the in the back group.

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* Kresge 502 Cart: And we're looking at an absolute scale here. The absolute number of deaths

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* Kresge 502 Cart: was a lot higher that were prevented among flattened. So I think that's awesome. What we see overall similar similar trends. But differences in absolute magnitude.

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* Kresge 502 Cart: so changes in prostate cancer mortality. By the way, don't just have something to do with screening. These are data from a bunch of European countries. Over a century before Psa screening was available. And, as you can see, there are huge changes actually up to 5 fold in the same country of prostate cancer mortality rates.

28:02

* Kresge 502 Cart: Why could that be

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* Kresge 502 Cart: curious about the answers? Because I don't know the answer. And

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* we have 2 people who know answers. They're shaking their heads, too.

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* Kresge 502 Cart: so we don't totally know. But let's think about together. What? Why could this be? What could? What could be going on here?

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* Kresge 502 Cart: And we see such changes for other cancers, too, not always in the same direction, with the same patterns, though

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* Kresge 502 Cart: the curve for breast cancer looks actually very similar. The curve for stomach cancer looks very different. It's just gone down or the curves for stomach cancer, I should say

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* Kresge 502 Cart: I'm just guessing is previously like in my team

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* Kresge 502 Cart: for 2010, like very few prostate cancer, are actually diagnosed. And so as your diagnoses sensitivity or or

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* Kresge 502 Cart: becomes more accurate and more people get diagnosed, they die from prostate cancer.

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* Kresge 502 Cart: That is a great explanation. And that is certainly one. I think that is one

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* Kresge 502 Cart: reasonable contributor, that

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* Kresge 502 Cart: it's always a problem in these long-term comparisons. Basically medical care changes our ability to even diagnose it

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* Kresge 502 Cart: did change even the diseases that we think exist. Change over time because we are learning of new diseases. We're splitting up the same disease into into more than more and more categories. So I think that's a great explanation. It may not be the entire explanation and to to come back to that example of gastric cancer at which I had the slide.

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* Kresge 502 Cart: Everything goes down so people sort of we wouldn't need to say. People knew how to diagnose stomach cancer, but they didn't know how to diagnose. Prostate cancer is a cause of death. So it's certainly contributing.

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* Kresge 502 Cart: But it may not be the only explanation other.

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* Kresge 502 Cart: Could there be other explanations? What do you think?

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* Kresge 502 Cart: I'm actually just staring at my next slide here, which is to your point. So maybe let's look at this together. And this is about how well do we actually know that someone died of cancer?

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* Kresge 502 Cart: And well.

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* Kresge 502 Cart: this is a study that tried to find this out. So. autopsies. I already showed you one autopsy study. This is a town on the eastern border of Germany, called Garlitz, on

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* Kresge 502 Cart: in 1,987. In this town I actually grew up an hour away from. So in 1,987. There were 1,060 people who died in that town of Gurlitt. I think there were about 100,000

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* Kresge 502 Cart: people, but

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* Kresge 502 Cart: And so there were 1,060 people, and out of those 1,060 people they were able to do an autopsy on 1,023. So 97%. So that's how many autopsies do we do? Currently, in the United States, when people die here, what percentage of people get an autopsy.

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* Kresge 502 Cart: Or let's say, how many don't about 97%. Actually. So it's something that we don't do any longer. And of course they did that here, basically for research purposes. But the autopsy rates were a lot higher back then.

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* Kresge 502 Cart: So let's exactly to your point. Did these people actually die of prostate cancer were able to to find that we're able to to to define that. So what they did, they tabulated what the death certificate said, what people were dying from, which is our usual cause of of cancer, mortality data. And then in the columns here, they're showing you what the cause, what the category of causes of death was based on

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* Kresge 502 Cart: on the autopsies that they did for the purpose of the study. So there were 199 people who were said to have died from neoplasms on their death certificate. So basically, if I'm

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* Kresge 502 Cart: whom cancer and you would assume from metastatic cancer. Of those 199 people, 178 were found to have died of cancer on their autopsy.

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* Kresge 502 Cart: So actually a pretty high, positive, predicted value.

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* Kresge 502 Cart: considering like this is why do I look on

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* Kresge 502 Cart: they didn't have computer tomography. They didn't have a lot of. There was no Psa. There were lots of things this in just pass it, of course, but there was lots of medical care that wasn't available.

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* Kresge 502 Cart: There were 30 people here who were said to have diagnosed have died of heart attacks on near embolisms and so forth. And they actually died of cancer based on the autopsy. So the sensitivity

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* Kresge 502 Cart: of the death certificate wasn't perfect. So there was actually more cancer. And it's often been described that cardiovascular disease in older people gets slightly over diagnosed, and these discrepancies that they saw were particularly

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* Kresge 502 Cart: oh.

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* Kresge 502 Cart: so to your point, there is definitely room for some of the differences over time if medical care gets more accurate to explain these things. But it doesn't seem like we're not seeing that the majority of cancer causes on the death certificate were wrong, at least in the in one town in Eastern Europe.

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* Kresge 502 Cart: Great! Let's quickly look back at these. What else could be changing over time?

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* Kresge 502 Cart: Yeah, yes, forward

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* Kresge 502 Cart: compared. I know this is decades ago, but compared to other countries

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* Kresge 502 Cart: in Europe, and I know the comparison is not really fair to the Us. But how does determine

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* Kresge 502 Cart: the cause of death? How can you intervene to the Us. Is it better or worse? Just to kind of generalize, although it's hard, but just.

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* Kresge 502 Cart: that's a good question, and a very, very tough one, because in order to have a good answer for you, I think we would actually need this type of study?

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* Kresge 502 Cart: Yep, yeah. And vice versa in a country that might be lower resourced. And so how good is it there

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* Kresge 502 Cart: having that comparison.

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* Kresge 502 Cart: seeing if it's like that there that help me in other countries that are not like, you know. And then, even like in a country like us, if you're diagnosed, maybe, or if you die at mass, general Hospital versus if you die in a local community hospital, is that the same?

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* Kresge 502 Cart: I don't know. Maybe maybe not.

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* Kresge 502 Cart: I wish I had a quantitative answer to you. I have anecdotal answers for this

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* Kresge 502 Cart: death. Certificates filling them out are not necessarily anyone's primary priority, because

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* Kresge 502 Cart: physicians typically care about living patients and people die

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* Kresge 502 Cart: in the middle of the night in the intensive care unit, or wherever it may be, but not necessarily. The death certificate may not reflect the entirety of what we know about them medically, even in life. Then, of course.

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* Kresge 502 Cart: yes, in theory, Germany, a well resourced country and so forth. This was Eastern Germany before the reunification services behind the Iron Curtain. There wasn't a lot of technology, it was medical training, but there were no American textbooks or something, so it may not be the Germany of of today. And then, even in the Germany today, I can tell you that

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* Kresge 502 Cart: for grandparents, I can tell you that Alfor died with a cause of death that was completely wrong. I don't know. That's an anecdote, but even in a very highly resourced country. So

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* Kresge 502 Cart: yeah, for example, what happens like those patients cancer.

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* they have like high.

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* Kresge 502 Cart: That's how they work.

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* Kresge 502 Cart: Yeah, yes, very good. So we can spend the next

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* 90 min on the classifying causes of death. But this is exactly people die because of cancer, because cancer creates havoc in the body, and cancer creates havoc in the body in terms of blood clots, for example, and that causes a polyamorous one. That's what people ultimately die of, but that is the

37:56

* Kresge 502 Cart: immediate cause of death, and it shouldn't be the one on the death certificate, because people would not have had. The argument is, people would not have had

38:17

* Kresge 502 Cart: this this black client had they not had the cancer. So the underlying cause of death is actually cancer. And across countries to your point about comparisons. That's how ICT classifications of death are to be performed, says the who. So that is always the underlying cause of death.

38:27

* Kresge 502 Cart: So, for example, during the COVID-19 pandemic. There was a lot of arguments about is COVID-19, a common cause of death, and the argument was well. These people were dying actually of heart attacks, while they also had Covid when they were in the hospital. Yes, but they wouldn't have been in the hospital on a ventilator and then gotten a heart attack, had not had Covid so who again said, Covid, is the cause of death, because it is the underlying cause of death.

38:53

* Kresge 502 Cart: Great I didn't expect to talk about Covid. So let's get back to prostate cancer and get back to the United States in 2,023. I updated everything about this slide except the title, and it should be 2024, those numbers actually, so these are estimates actually are from based on data from a few years back.

39:24

* Kresge 502 Cart: about 300,000 people are expected to be diagnosed with prostate cancer in the United States this year, which is about almost a third of all new cancers in men.

39:49

* Kresge 502 Cart: and about 35,000 deaths are expected this year, which is about one in 9 of every death from cancer. So both for incidence and for mortality, a major bird. So those were the population statistics and individual level statistics is that 13% lifetime risk that I quoted earlier and one in 40 risk

40:03

* Kresge 502 Cart: of dying from prostate cancer.

40:32

* Kresge 502 Cart: So which also means these numbers also trade translate to a substantial prevalence. There are 3.6 million people in the Us. Right now. Will have a diagnosis of prostate cancer, and who may have been completely, successfully treated, and may never see their

40:36

* Kresge 502 Cart: deal with prostate cancer again. But we'll still undergo monitoring and so forth. But about 100,000 to 150,000 of them. We don't exactly know how many

40:56

* Kresge 502 Cart: are actually living right now with metastatic prostate cancer.

41:08

* Kresge 502 Cart: So, coming back to our racial disparities, and I think that was hard to overlook in the previous slides, even from trends. These are again

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* Kresge 502 Cart: racial categories. Now we're at 5 racial categories, the ones that the census

41:24

* Kresge 502 Cart: users, plus a group separately for Hispanic. And what you see is

41:31

* Kresge 502 Cart: very, very strong disparities in prostate cancer mortality. If White were the reference group than the mortality rate in black men were 2.1 fold greater. But if Asian were and Pacific Islanders in one group were the reference category. Then we're talking about a fourfold difference. So

41:38

* Kresge 502 Cart: so huge

42:03

* Kresge 502 Cart: disparities. And they're only in gastric cancer. As big as

42:05

* as a prostate cancer.

42:12

* Kresge 502 Cart: So why is that, and the next heart is about inherited genetics. That is not to say that inherited genetics are the only cause.

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* Kresge 502 Cart: And, in fact, I'd like to look together at this

42:27

* Kresge 502 Cart: graph here together with you, and see what we make out of these numbers here together. These are.

42:34

* Kresge 502 Cart: This is a great example of a migrant study where. looking at prostate cancer incidence before psa screening messed up the picture

42:42

* Kresge 502 Cart: prostate cancer incidence between.

42:57

* Kresge 502 Cart: I've been in Japan

43:02

* Kresge 502 Cart: the first generation of migrants to Hawaii, the second generation and white Hawaiians.

43:05

* Kresge 502 Cart: And we're seeing that for prostate cancer on the right and then stomach and breast cancer in the left and in the middle.

43:17

* Kresge 502 Cart: what do these numbers tell you? How do you interpret them?

43:30

* Kresge 502 Cart: Let's start with a stomach cancer on the left, because that is the most clear cut.

43:52

* Kresge 502 Cart: Yes.

44:04

* migration.

44:10

* lifestyle factors.

44:15

* Eric.

44:19

* Kresge 502 Cart: Yeah, I'm I'm walking

44:22

* Kresge 502 Cart: complex.

44:28

* So

44:35

* Kresge 502 Cart: great summary of the data. And you're exactly pinpointing 2 of the Major, I don't know competing, but major explanations. One is. Migrants

44:37

* Kresge 502 Cart: a generation later are genetically the same as the country they're coming from. As a population even 2 generations more than that.

44:53

* Kresge 502 Cart: So there must be something that's not genetic that's changing. And yes, we know each pylori infections are

45:04

* Kresge 502 Cart: the major modifiable factor for stomach cancer with hygiene and more antibiotic exposure on immigration. That is one of the contributors there

45:14

* Kresge 502 Cart: and then there are probably genetic differences. What about breast and prostate. There's one thing that I don't want to get you too tripped off. Is this difference here between these 2 bars here? That's maybe hard to interpret.

45:31

* Kresge 502 Cart: We're seeing the opposite pattern. We're seeing that on immigration to the United States

45:55

* people without a change in their genetics so suddenly, you have a substantially higher risk within a generation

46:02

* Kresge 502 Cart: than white Hawaiians.

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* Kresge 502 Cart: At the same time, even within 2 generations, for both breast or prostate cancer.

46:15

* Kresge 502 Cart: the levels of risk don't reach that of the

46:23

* Kresge 502 Cart: of the other archbishop.

46:29

* Kresge 502 Cart: That is summary that

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* Kresge 502 Cart: everyone more or less could agree with.

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* Kresge 502 Cart: Okay, then let's try to understand why that could be

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* Kresge 502 Cart: another hint that there is something genetic about prostate cancer is, we know that Osteo runs in families.

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* Kresge 502 Cart: men who have a brother or a father who has a diagnosis of prostate cancer have a 2 to 4 fold higher risk of prostate cancer themselves, and men with a mother or sister with breast cancer, breast cancer have a 1.5 to 1 point sevenfold higher risk of prostate cancer.

46:52

* Kresge 502 Cart: The other part piece of evidence comes from twin studies. So where twin studies

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* Kresge 502 Cart: study a monozygotic and dizygotic twins who share the environment in which they grow up in.

47:23

* Kresge 502 Cart: And they share all their genetics or share half of their genetics.

47:33

* Kresge 502 Cart: Okay?

47:40

* Kresge 502 Cart: And what we see from there is that plastic cancer melanoma isn't on the graph here, but plastic cancer and melanoma are the most heritable cancers due to genetic factors when we're partition into genetic factors and shared environment.

47:42

* Kresge 502 Cart: And the Y axis shows us something that we'll see in the next few slides is how much of that genetic risk can we already, with genetics from today explain this? Actually, the number has actually slightly increased since this slide. And I'll show you the latest numbers

48:03

* Kresge 502 Cart: when we talk about genetics. And we've heard a bit about this before we talk about rare variants and about common genetic variation. There's a lot of variation between our own genomes is where

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* Kresge 502 Cart: we're all different. At millions of sites in our in our genome

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* Kresge 502 Cart: for cancer risk, there are 2 things that are that are relevant.

48:44

* Kresge 502 Cart: One is

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* Kresge 502 Cart: these rare but highly Pentrans mutations. So they have a strong effect on cancer risk.

48:51

* Kresge 502 Cart: Those probably explain about 5 to 10% of cancer. So those are the Baraka one and 2 for breast ovarian and prostate cancer. So

48:59

* Kresge 502 Cart: they're rare. But when an individual has them. The risk is substantially elevated.

49:11

* Kresge 502 Cart: and the second part is common genetic variation. So

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* Kresge 502 Cart: we all have common genetic variation, because that reference genome is not a real person

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* Kresge 502 Cart: on.

49:31

* Kresge 502 Cart: and the effects of those common things that are slightly different between people. They're small individually, but when we sum them up over the entire genome. We can create scores that at the end of the day are actually quite useful for risk stratification, as I'll show you in a second.

49:33

* Kresge 502 Cart: These studies are genetic epidemiology studies. And I just wanted to show you how they look like this is the

49:52

* Kresge 502 Cart: second last big, genome, wide association study for for prostate cancer. It's a case control study. It's not the kind of case control study that you may learn in. And IP. 2, one. It's just cumulative incidence sampling like whoever has prostate cancer as a diagnosis is a case into.

50:00

* Kresge 502 Cart: and people of a certain age who don't. By then they're in control. And then these studies do logistic regression and adjust for age. And that's the analysis, basically. But it's huge numbers.

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* Kresge 502 Cart: And the other part, why, I'm showing you this study is, these studies are still to this day predominantly European ancestry, as you can see, based on the case and control counts compared to

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* Kresge 502 Cart: other continental origins.

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* Kresge 502 Cart: This is now the latest prostate cancer. Jiwaz. There are 451

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* Kresge 502 Cart: variants,

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* Kresge 502 Cart: single nucleotide polymorphisms or snps for prostate cancer risk that are statistically highly significant, some of them with a P value of 10 to the minus 600. So we're pretty sure that they're associated with prostate cancer from humongous sample sizes

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* Kresge 502 Cart: talk about in a second, how relevant actually, that 451 number is.

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* Kresge 502 Cart: And again, individually, the effects of each variant are very small, so that P value is really driven a lot by the fact that we have huge sample sizes.

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* Kresge 502 Cart: But when we then summarize those 451 variants in a single score. That's the Polygenic risk score. And this polygenic risk score you can

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* Kresge 502 Cart: what this study does here. It cuts it in half. It says, half of the population has a Prs below the medium, so 0 to percent, and the other half of the population has a Prs of 50 to to 100%.

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* Kresge 502 Cart: And what we can see is that the vast majority of prostate cancer is happening among people with polygenic risk score above the media. So 4 people who have a family history of prostate. So this is a combination here. So in fact, this low risk group here low risk. And no family history is about 40% of the population. And this other

51:59

* Kresge 502 Cart: group here is about 60%. So it's not really a higher risk group, because 60% of the population wouldn't necessarily qualify it higher as high risk. But what we can see here is there's at least 40% of the population that has a very, very low risk.

52:25

* Kresge 502 Cart: And this is for prostate cancer diagnosis and sort of to your point. A diagnosis is sort of would think comes before death. So people who don't get diagnoses of prostate cancer also don't

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* Kresge 502 Cart: die from us. So among people who don't have a cancer diagnosis, yet polygenic risk scores are very, very strong predictors, and they will probably be used clinically

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* Kresge 502 Cart: within the next few years, increasingly more, not just for prostate cancer. But as you saw in that graph that I showed you prostate cancer is is one of those examples where they perform the best. There are many common conditions where they don't perform as well as what we're seeing on this graph here, looking at the panel on the left.

53:08

* Kresge 502 Cart: I want you to think about the prevalence is that autopsy that you saw

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* Kresge 502 Cart: even in, say, ages 40, 50 years old? How how do those autopsy prevalences compare to these

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* Kresge 502 Cart: lifetime risks for prostate cancer, say, by age.

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* Kresge 502 Cart: 60 or 70.

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* Kresge 502 Cart: Thank you. What are you going to say? Something? No, no, that's great. It's interesting. Watching this talk and thinking like, oh, this is really interesting.

54:00

* Kresge 502 Cart: Do you remember what the prevalences were in the autopsy? Said, the percent of men who seem to have prostate cancer

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* Kresge 502 Cart: save in that age 40

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* Kresge 502 Cart: 16.

54:23

* Kresge 502 Cart: What's that? Yes, about 30%. And so if you look at even at the group that had the highest polygenic score, the greatest genetic risk. What was their lifetime risk?

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* Kresge 502 Cart: Maybe

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* Kresge 502 Cart: maybe 8%

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* 2.

54:47

* Kresge 502 Cart: There's like of death. Yeah of death from prostate cancer. So yeah, so sort of to this point the majority of what could be diagnosed is not being diagnosed. And even this year is a very highly screened population. 80% of them actually got Psa tests.

54:48

* Kresge 502 Cart: Not an insignificant percent of those cases were

55:12

* Kresge 502 Cart: bad policing scores. So it wasn't like they were just. oh, these really benign looking histologically cancers, but there was probably a third of them. I think, that were

55:16

* Kresge 502 Cart: higher degree tumors, which is super interesting. So why aren't they causing problems?

55:29

* Kresge 502 Cart: One thing about the pledging risk force that I want to emphasize is there are genetics there are in genes. There are lots of functional studies, but there's nothing

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* Kresge 502 Cart: magic about there being exactly that number. And like they're not necessarily cause. This is a prediction exercise. And this is from the previous Jiwas, which is the 269 Snps for prostate cancer. Now we're at 451.

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* Kresge 502 Cart: But what this is is fitting a model and looking at how many snps make the statistical significance threshold. And how good does the Auc get? And, as you can see, with the data that they had a few years ago the Aeoc didn't get better anymore. Once they added, more snps into the model. But it doesn't mean that these things here don't cause prostate cancer any longer.

56:09

* Kresge 502 Cart: It's just like it's a prediction exercise.

56:32

* Kresge 502 Cart: So now.

56:39

* Kresge 502 Cart: I'd like to ask you a really tough question for that. You need your phones, or you can type in this number here on the bottom. So we've talked about from the twin studies that we know that 57% of prostate cancer risk is due to genetics. With that 95% confidence above 51 to 63.

56:40

* Kresge 502 Cart: What do you think is the best interpretation of those data?

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* Kresge 502 Cart: So please do both. Because

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* Kresge 502 Cart: curious about your thoughts.

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* Kresge 502 Cart: Is it opening more good?

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* Kresge 502 Cart: I'll do, too, so I will get at least one wrong answer.

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* Kresge 502 Cart: Great! Keep going.

57:41

* Good distribution so far

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* Kresge 502 Cart: out of the 3 people. I can tell that there are more people with the phone hands.

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* Kresge 502 Cart: Not every epidemiologist can count. But I can't count that far.

58:02

* Kresge 502 Cart: so there don't feel like this is not an exam, so you don't need to be sure about what you're answering. Just pick one that sounds most reasonable to you.

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* But please do.

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* Kresge 502 Cart: You're all seeing the the distribution.

58:35

* Kresge 502 Cart: Hmm.

58:51

* thanks. Ok. A couple more, and now we're done. If you haven't voted yet, please do. And then we can give God.

58:56

* Kresge 502 Cart: Great. Okay, let's call it a day. So 69% of you thought that non-genetic factors are were difficult to explain. But they could explain up to 43% of prostate cancer risk.

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* And 25% of you said that genome, wide association studies

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* Kresge 502 Cart: of common genetic appearance will ultimately explain likely less than 57 genoc. The other 2 choices were not as popular.

59:33

* and

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* Kresge 502 Cart: I think you did just as well as

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* Kresge 502 Cart: when I showed the same exact, same answer to a group of urologists who've been studying prostate cancer for for many years. And

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* Kresge 502 Cart: so that's great to see.

1:00:04

* Kresge 502 Cart: I will still argue

1:00:07

* Kresge 502 Cart: that the right answer is actually this one.

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* Kresge 502 Cart: And does anyone want to give the motivation for? Why you picked that answer and not the others, and I know this was a really hard question.

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* Kresge 502 Cart: and I fooled you with a condom in the bottom. I take the blame for that. and I changed my answer to this one.

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* Kresge 502 Cart: So

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* Kresge 502 Cart: it's the key word. Here is comedy rather than

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* Kresge 502 Cart: to your genetic variants, and it's getting back to identify yet high risk of dying from prostate cancer rather than

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* Kresge 502 Cart: having prostate cancer, but dying from other. That was what I thought when I changed my answer.

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* Kresge 502 Cart: there's a point that it says common genetic variants. So what I showed you a few slides ago is that 57% of prostate cancer risk to take the point. That interval is sort of the most likely estimate are due to genetics.

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* Kresge 502 Cart: But there is common genetic variation, and then there is rare genetic variation. So it's likely that

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* Kresge 502 Cart: it's not all common genetic variation. So it's not all snips. But there is. There are things like Rocket, one, Brachit, 2, and so forth. And they're they're not rare there there as causes of cancer, 10% of cancers are probably caused by them. So

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* Kresge 502 Cart: that's why this is actually a thought. I'm giving you the right answer.

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* Kresge 502 Cart: At least, I thought.

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* Kresge 502 Cart: why is this one not the right answer? This is the one where it tricked you with a with a confidence.

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* and I'd love to walk you through.

1:02:04

* Kresge 502 Cart: But this goes back to the 1,900 thirtys to

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* big debate in

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* Kresge 502 Cart: actually the camp of the Eugenesis, who thought that humanity could be improved by basically killing people who looked

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* Kresge 502 Cart: genetically to be not the ones that we thought would be the most desirable, most healthy, and one of the leading statisticians run. Ronald Fisher, was their leading proponent from a statistics perspective to say, because

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* Kresge 502 Cart: this is the genetic contribution to disease. And this guy here Leslie Hawkman, was

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* Kresge 502 Cart: very vocal in in pointing out that we can't partition diseases as being genetic or non-genetic.

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* Kresge 502 Cart: and that has huge implications for what we do about them. For one, we shouldn't be killing people, of course, but we should be thinking about what we can do on

1:03:00

* Kresge 502 Cart: about the environment. So the genes and the environment don't sum up to 100%.

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* Kresge 502 Cart: So I fooled you by giving you, even though comfortable, with the same development that it seemed like you could subtract one from 100% and get the

1:03:18

* Kresge 502 Cart: every condition is always so. I don't know if it might be the sufficient component cause models. So I find them actually useful to to look at here.

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* Kresge 502 Cart: Each of them is one person who got on a disease, and maybe this is prostate cancer and made up some causes here for these 3 people in our population with 3 people and the Polygenic risk score is a component cause of all of them here it's a necessary cause, because in all of them. Maybe cosmic relation is, too. Nobody knows.

1:03:49

* Kresge 502 Cart: I don't know if cosmic radiation causes prostate cancer, you won't be able to say that's not the case because everybody's exposed, so we can't tell.

1:04:11

* Kresge 502 Cart: And then I put some, maybe more credible risk factors there, too. So while we make the counts here. we're seeing that an environmental risk factor. Cosmic variation is responsible for 100%. And Ips, a genetic factor is too.

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* Kresge 502 Cart: And we can even act on these. We could maybe eliminate cosmic radiation, which is nonsense.

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* Kresge 502 Cart: but that would get rid of all of it.

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* Kresge 502 Cart: or we could. And this is something that is being clinically done, we may have better interventions that people with a particular genetic condition benefit from this is what we do with Brca cures and breast cancer prevention, for example, mastectomies

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* Kresge 502 Cart: could think, well, maybe it's a prostatectomy need for it

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* Kresge 502 Cart: for prevention of prostate cancer. So there, we've altered, or we've acted upon knowledge of a genetic condition

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* Kresge 502 Cart: which has changed nothing about the contribution of the environment in that case of prostate cancer, because maybe this case wouldn't have occurred had this person been physically active.

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* Kresge 502 Cart: So to maybe bring these things together and really then get into what can we do about prostate cancer? We could think like, Oh, maybe the simplistic views here. The first one are germline respirants. They cause a prostate cancer diagnosis that we've got to treat it. Otherwise people die.

1:05:39

* Kresge 502 Cart: It's maybe not as that ignores a few things, and I think prevention from epidemiology perspective. We have more shots at cancer prevention. And one concept that we'll talk about is there's indolent. And there's aggressive prostate cancer. There are causes are different. Germline variants increase the risk of prostate cancer, but non genetic factors

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* Kresge 502 Cart: increase particularly the risk of aggressive prostate cancer. And then we can screen

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* Kresge 502 Cart: to reduce the stage of diagnosis. And then there are issues around treatment, access per and all of these things are relevant, not just for prevention in general, but particularly also for reducing racial disparities in in cancer, because

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* Kresge 502 Cart: otherwise the argument go as well among African Americans. It's all genetics. So all we can do is

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* Kresge 502 Cart: is increase access to treatment. But that would leave still a higher incidence. So it would still leave a higher disease growth.

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* Kresge 502 Cart: So what are those risk factors to talk about the first component here and those risk factors active along the life course. We've seen that cancer initiation is something that comes very early in life. We've seen among year olds that there is a lot of prostate cancer already. So we want to prevent that from happening. While that's

1:07:06

* Kresge 502 Cart: we'll probably need to think about things that act very early in life. But we also need to think about those cancers

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* Kresge 502 Cart: are clearly not relevant among year olds. Yet so there must be things that are happening during the remainder of the life course that make these cancers progress. Further, so that part is also important in genetic factors, or they act throughout life.

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* Kresge 502 Cart: So for total prostate cancer, which means a diagnosis of prostate cancer, regardless of what stage it is, what rate it is. These are what people would agree on as a risk factors. And that list is what people have a much easier time agreeing on

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* Kresge 502 Cart: here. African descent and genetic risk close Ir are separated. But

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* Kresge 502 Cart: that really we're talking about the same thing we're talking about when we're talking about genetics, and then height is

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* Kresge 502 Cart: a strong risk factor for prostate cancer. And actually, other cancers, too. So this is the meta analysis

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* Kresge 502 Cart: and height is actually interesting with regards to that life course that I just showed you. Because when do people get taught? While during puberty, so very early in life

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* Kresge 502 Cart: when both genetic and environmental

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* Kresge 502 Cart: conditions. So how much food is available, what kind of food, how much dairy do people consume? Those things do influence on bike gain, and they also influence.

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* Kresge 502 Cart: presumably the growth of the prostate. And we've seen that they influence the risk of prostitute.

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* Kresge 502 Cart: So all of this to suggest that this is one period during which risk factors are already acting on

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* Kresge 502 Cart: causing a cancer that will only become clinically apparent typically

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* Kresge 502 Cart: in people in their'. So an example of a very long lag time that concept that people have probably beaten into you already over the course of the time of this course, that in cancer epidemiology. There's often a long time between when somebody is exposed and when we see the effect of an exposure.

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* Kresge 502 Cart: So now let's imagine we would do a cancer epidemiology study, not of prostate cancer, but of every cancer down there like

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* Kresge 502 Cart: talking to, maybe not your grandparents, but your grandparents' grandparents, when they would be asking, what cancers did your parents die from? And they would be saying something like, Don't know exactly. Put something down there. That's sort of

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* Kresge 502 Cart: an example of misclassification. But it's the example of misclassification that you'll see we're doing in research still today. If we did that, if we threw them all into one bucket

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* Kresge 502 Cart: as risk factors. Out of that bucket would come age, race, and family history. Maybe we would get a few other risk factors because they're very, very strong risk. Factors

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* Kresge 502 Cart: come, maybe crip autism. So not understand the testicle for testicular cancer. Maybe each Pv has a very strong risk factor for a necessary factor for for cervical cancer

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* Kresge 502 Cart: may be obesity, because it's a very strong risk factor for kidney cancer from Demetrius cancer.

1:11:04

* Kresge 502 Cart: And we actually don't do throw all cancers into one bucket any longer for breast cancer. They're clinically used. Subtypes, molecular subtypes based on molecular tests done in tumor tissue. Those are clinically used because their therapy is attached to them, and from those we learn that

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* Kresge 502 Cart: being pregnant more often decreases the risk of basically hormone receptor, positive breast cancers. but increases the risk of triple negative breast cancer.

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* Kresge 502 Cart: And if we throw all breast cancer into one bucket. we put Cnola Association.

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* Kresge 502 Cart: Oh. we still throw mostly prostate cancer all into one bucket, and that is one of the explanations why the list of risk factors that people can universally agree on

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* Kresge 502 Cart: is shorter than for for other cancers, so which in turn also means there's a lot of good epidemiology that we can still do by

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* Kresge 502 Cart: by getting beyond our

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* Kresge 502 Cart: growing things together that don't belong together. So we're not

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* Kresge 502 Cart: getting at least agreement out of that bucket again. So this is the list of risk factors for advanced or fatal prostate cancer. So those are prostate cancers that are no longer confined to the prostate cancer that people die from. And all of a sudden that list gets a lot longer, because if you keep searching for risk factors for

1:12:21

* Kresge 502 Cart: total plastic cancer, those are cancers, while everything is confounded by Psa screening, because people get screened for cancer when they're interested in health maintenance. People who are interested in health maintenance

1:12:44

* Kresge 502 Cart: are healthier and psa screening detects certain types of prostate cancers better than others.

1:12:57

* Kresge 502 Cart: But when we talk about cancers that have the potential to metastasize the potential to cause death, then that is a different subset, and these are

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* Kresge 502 Cart: possible or probable risk factors.

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* Kresge 502 Cart: I'd like to show you one example of physical activity and prostate cancer.

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* Kresge 502 Cart: Now, here, we're not looking at the outcome separately by whether the cancer has metastasized or not.

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* Kresge 502 Cart: We're looking at malikar subtypes of prostate cancers because they exist in prostate cancer just like they exist in other cancers and other cancers. I just mentioned asteroid receptor or hormone receptors that is, in breast cancer.

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* Kresge 502 Cart: in colon cancer, microsatellite instability, each Pv positive added neck cancer. So those are the common clinically used subtypes. Again, because there are therapies attached to them. That's why there's also a lot of studies, because everyone who has a diagnosis of these cancers. That information is on the medical record for prostate cancer. There's no information about subtypes on the medical record right now.

1:13:53

* Kresge 502 Cart: but there are molecular subtypes. And indeed, the gene fusion between 2 genes er g and tempus 2

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* Kresge 502 Cart: is about present in what half of all prostate cancer. So it's not like a necessary thing to study, and as you can see here, across quintiles of vigorous physical activity.

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* Kresge 502 Cart: the association with urb negative prostate cancers is completely null versus. There is at least the suggestion of a protective association among erg positive prostate cancer.

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* Kresge 502 Cart: Now we see similar things to go back to the earlier classification for advanced and lethal, so advanced increased stage lethal meaning metastases or prostate cancer death. Again, that's where

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* Kresge 502 Cart: associations between protective

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* Kresge 502 Cart: factors and risk factors and those prostate cancer outcomes are even detectable.

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* Kresge 502 Cart: Interestingly, for these results, the results are even stronger among men who were all undergoing Psp screening.

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* Kresge 502 Cart: Why is that that important? I would particularly want to look among highly grief men as opposed to just everyone

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* intend to be wild.

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* Kresge 502 Cart: Yep. And why? How would that influence the results of the study

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* Kresge 502 Cart: I was working. If you have. is that what you're asking how to effect the testimony, or what were the results here? Yeah, yeah, I think you would under estimate.

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* Yeah.

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* Kresge 502 Cart: Because the

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* Kresge 502 Cart: in Egypt.

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* Kresge 502 Cart: you know, protected behaviors like they would like to

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* reduce the risk.

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* Kresge 502 Cart: Yeah. So it's an example of confounding exactly as you're as you're describing. So more physical activity goes along with more Psa tests so leading to

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* Kresge 502 Cart: diagnosis of cancer that otherwise would have not been diagnosed, but

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* Kresge 502 Cart: The causal effect of

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* Kresge 502 Cart: maybe preventing prostate cancer could be masked by that. So that's one part of why. And it's a very important part that's confounding the other part is probably something around effect modification, that if you screen at regular intervals you're more likely to pick up a cancer that has been sitting there all alone.

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* Kresge 502 Cart: So it it peaks up cancers that are slower to grow, and are. and are more more indolent as opposed. So you can imagine when you do a screening test. Maybe every other year cancers that grow very quickly

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* Kresge 502 Cart: may become clinically apparent between those 2 on the screening of faces. So that's for length time.

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* Kresge 502 Cart: So for

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* Kresge 502 Cart: so the other part about lifestyle, we just quickly talked about on physical activity. But of course there's other modifiable risk factors. Now the big question is, I've argued with you that

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* Kresge 502 Cart: genetics and environment are not mutually exclusive. But what about people who have bad genetics meaning. There are higher risk because of genetics. Is

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* Kresge 502 Cart: is there cancer risk still amenable to prevention? So to walk you through here? This is a study again, stratifying people by their polygenic risk score. And again, as I've shown you before, the polygenic risk scores work really well.

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* Kresge 502 Cart: the lifetime risk of any prostate cancer type is something about 15% and goes up to 50% among people in the highest quartile and the same for metastases. So death, comprising cancer or substantial differences by genetic predisposition, just common genetic variants developed.

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* Kresge 502 Cart: So I said, this is one example of a healthy lifestyle score, so very.

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* Kresge 502 Cart: very basic things in a way very leniently defined.

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* Kresge 502 Cart: And now we're stratifying people into 12 different groups, essentially, people with very low, genetic risk, and people with quite high genetic risk, and some intermediate cancers. So maybe let's look at the extremes because they're most telling. There's very little prostate cancer among people with low genetic risk. So there's

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* Kresge 502 Cart: hard to say much.

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* Kresge 502 Cart: So that's an example of good risk. And there's a lot of prostate cancer. Now, we're looking at prostate cancer

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* Kresge 502 Cart: metastases and death here among people with a high genetic risk.

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* Kresge 502 Cart: However, when you then stratify people by lifestyle among people with higher genetic risk.

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* Kresge 502 Cart: you see that

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* Kresge 502 Cart: people with a healthy lifestyle have substantially delayed an onset of metastatic and fatal plastic cancer at much lower rates and lower lifetime rates. Whatever measure you want to know

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* Kresge 502 Cart: other

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* Kresge 502 Cart: you have concerns about what could be going on there.

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* Kresge 502 Cart: Could it be that people are genetically different, and they have a different lifestyle or something?

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* Kresge 502 Cart: Gotcha

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* Kresge 502 Cart: turns out. No, I'm first.

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* Kresge 502 Cart: We've done these studies for for a while. Now we can't make this go away and like it's been seen in other studies, too. This is not a result just for prostate cancer. This is something that we keep seeing over and over for different types of cancers, but also for genetic predisposition to other chronic, chronic, common chronic conditions. People at a high genetic risk

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* Kresge 502 Cart: are just as amenable to, or might benefit in relative terms just as much as people with low genetic risk. But in absolute terms, as you can clearly see from these primitive incidents, curves, their benefit is even much higher, because there's more happening.

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* Kresge 502 Cart: Ok, let's talk about screening as another means. And we've covered a lot of ground on screening already

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* Kresge 502 Cart: with meth. I've just not talked much about what Psa actually is. Psa is just a biomarker. It's a protein that's made by prostate. It's not made by prostate cancer necessary. It's made by B prostate. And that explains why it's not the perfect test.

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* Kresge 502 Cart: And it's often thought to be

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* Kresge 502 Cart: just a marker of prostate cancer. And initially, it was actually meant to be a marker just for measuring progression of prostate cancer, but was quickly repurposed for screening, for prostate cancer, which is, as you can imagine, a much bigger market.

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* Kresge 502 Cart: and there's

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* Kresge 502 Cart: it gets binderized. And when it reaches a certain level, then it typically triggers a biopsy of the prostate. Nowadays, also an MRI of the prostate.

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* Kresge 502 Cart: So what pse does is it buys us leap time and lead. Time means there are these 7 to 10 years between when there is prostate cancer that is easily tactical by Psa screening. And the time this cancer would be clinically diagnosed otherwise.

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* Kresge 502 Cart: And if we did the blood test, it shifts the diagnosis. Those 7 to 10 years work. So the effect of the screening is to make use of that lead time. So there's lead time bias. But screening actually buys us that lead time. And it's those 7 to 10 years during which

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* Kresge 502 Cart: screening can be beneficial. If there is a treatment that works better now as if we had waited those 7 to 10 years, and that's more important. But nobody should get screened if they don't have access to treatment, because then we're only harmed.

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* Kresge 502 Cart: There's been a lot of talk about whether prostate cancer screening works, and particularly in the United States, because the American trial showed that it didn't work.

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* Kresge 502 Cart: But it turned out over the years that actually the American trial had not worked because it was meant to compare Psa screening versus, not psa screening. It turned out

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* Kresge 502 Cart: that the intention to treat the analysis of that trial was completely misleading, because the people in the control arm had also gotten Psa script. So it was comparing a lot of screening to even more psa screening and even more psa screening was not beneficial.

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* Kresge 502 Cart: There was a European trial that did not have the same issue.

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* Kresge 502 Cart: And this trial has shown that Psa screening reduces

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* Kresge 502 Cart: the risk offered

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* Kresge 502 Cart: death from passive cancer by about 20%. So relative risk of point heat which translates into this risk difference of 0 point 1 injected at 16 liters.

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* Kresge 502 Cart: and the numbers needed to invite and to diagnose or higher.

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* Kresge 502 Cart: get them at first, but they're actually very similar to breast cancer. This is how mammography screening looks like, too. This is how many people do you need to invite. And this is then the number of people who need to be treated in order to prevent one death

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* Kresge 502 Cart: from this specific cost. So we actually discussed a recent article by Welch and Day in class together, which is really interesting in terms of thinking about swimming trials.

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* Kresge 502 Cart: cancer, specific death, etc. So very timely discussion. As you can see, this is a small contribution to all death, so it's hard, with this intervention to make it dent into death from any cause.

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* Kresge 502 Cart: but it works for prostate cancer and keep in mind. The absolute risk may be very different in a group at very high, absolute risk, to begin with. So no very high absolute risk to begin with, or risk ratio of 0 point 8 or a risk ratio of 0 point 8 actually may make a difference.

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* Kresge 502 Cart: but it may.

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* Kresge 502 Cart: For people who are low risk. To begin with, it may not be a good.

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* Kresge 502 Cart: What's the incidence?

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* Kresge 502 Cart: Greater issue for plastic cancer in the European trial. So in the trial that worked, comparing screening versus no screening. would you think it's 1.6 0 point 8 or

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* Kresge 502 Cart: completely null

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* Kresge 502 Cart: who votes for 8?

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* Kresge 502 Cart: One vote for A, who votes for B. You don't need to know. But what will you guess? I don't expect you to know

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* Kresge 502 Cart: on gas for a P. And he asks for a seat.

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* Kresge 502 Cart: We want to do a again. Yes, great. I love it so. Yes, screening detects cancer. So screening does detect more cancer. So that's exactly what we've seen. When we looked at the trends over time, that hump in prostate cancer incidence. That was Psa screening. That's exactly the effect of of what it does. It's not a colonoscopy where you move a precursor.

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* Kresge 502 Cart: And incidence actually goes, though, this is a test that detects cancer. So it makes incidence go up.

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* Kresge 502 Cart: Similarly, cervical cancer is another example, right?

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* Kresge 502 Cart: And because of these issues around, does it work? Does it not work

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* Kresge 502 Cart: you as preventive sources. Task force has been going back and forth about whether screening is recommended. And that's why you see these changes in incidents over time. And of course there are concerns about when you don't screen

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* Kresge 502 Cart: those decreases in prostate cancer mortality that we've been seeing now for a long time may not be continuum.

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* Kresge 502 Cart: I may be plateauing, but at the same time

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* Kresge 502 Cart: the sensitivity of the screening approach, so

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* Kresge 502 Cart: that Psa test, plus everything else that you do so, the screening program still needs to be better than what we're doing today, because, frankly, it is still driven by incentives that incentivize diagnosing and triggering more cases, despite everything that has been done

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* Kresge 502 Cart: so. And

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* Kresge 502 Cart: this is the effect that we're seeing on on survival. This relative survival is where we where we started.

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* Kresge 502 Cart: we started with relative survival of prostate cancer in the 1,900 seventys around 70 to

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* Kresge 502 Cart: 70%, just about where breast cancer was. And now it's at 99%. So it's a lot of progress.

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* Kresge 502 Cart: But it's both improvement in treatment because of screening. But it is also diagnosing lots of people who would not necessarily need to be undiagnosed.

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* Kresge 502 Cart: So with that, I'd like to and

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* Kresge 502 Cart: and summarize that prostate cancer is a major public health burden with strong racial disparities both for incidence and mortality, and those racial disparities are both, and always at the same time, due to genetics as well as to non genetic factors.

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* Kresge 502 Cart: Puberty is a critical period for exposures that affect prostate cancer. But then, of course.

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* Kresge 502 Cart: risk factors along the life course have an effect on to

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* Kresge 502 Cart: the risk. Factors for prostate cancer are a lot more controversial. This is a cancer that really still needs a lot of work. You can't do this case control study with a couple 100 people. Ask them, are you a smoker? And you've got 90% of your population as a fraction right there, as people did in the for lung cancer. This is really a cancer that is a lot harder to

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* Kresge 502 Cart: to study, but also a lot more interesting. I personally. Thank you. Please.

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* Kresge 502 Cart: those risk factors are really for advanced prostate cancer, the ones on this one pattern that I didn't mention for the risk factors that we've seen insulin and growth factors.

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* Kresge 502 Cart: both during puberty as well as for the other risk. Factors during the life course have a big impact. And we talked about Psea screening. It reduces on prostate cancer mortality and really profoundly impacts

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* Kresge 502 Cart: the observed burden of prostate cancer. And it is.

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* Kresge 502 Cart: as always, we've looked at prostate cancer very early in life, that it is a disease of older men. So that is.

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* Kresge 502 Cart: that is important in all considerations. Raw treatment. Great. Thank you. We're at the hour

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* here for questions.

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* Kresge 502 Cart: I know we're a little over time. So I was saying, maybe if we don't have other questions specifically, you'll be here. And you also have Dr. Stubbs email address as well, exciting projects for people looking for a research project.