* Just

0:06

* okay.

0:12

* Kresge 502 Cart: Oh, whoops! Go back to the zoom. Alright

0:16

* Kresge 502 Cart: good to see you all. We just wanted to start today to quickly talk a little bit more about the assignment. Hopefully, you've all had a chance to review the document in detail, and you've been meeting with the group component. But both components, the individual and the group component are due on Tuesday, individual component, due at 1159 next Tuesday.

0:55

* Kresge 502 Cart: and the group component, regardless of which day you're presenting. The slides are due on Tuesday. Just so. Everyone is due at the same time. But we did put up the schedule, so you should all know and be prepared.

1:19

* Kresge 502 Cart: What we're looking for. We just wanted to quickly outline for the individual. Write up truly what we're looking for is this list here. So just making sure kind of checking off as you're going through and writing this all up in your own words, using these databases to get at the descriptive epidemiology and kind of checking off each of these individual components. This should be doable in 2 pages single-spaced, but we do give you a little bit of wiggle room if you

1:36

* Kresge 502 Cart: want up to an extra page that's totally fine, but you should be able to do it in 2 pages single space without any worries.

2:04

* Kresge 502 Cart: Anything to add. Michelle. Well, I mean, does anyone have any questions concerning the individual write-up

2:12

* Kresge 502 Cart: is 2 pages the minimum, or would have less

2:23

* Kresge 502 Cart: if you can do it, unless sure as long as you're hitting all of these points that we've outlined. That's great. If you do it in less than 2. That's awesome. Yeah, we've had. Previously the assignment was 2 pages, and we asked, people were asking for more room. So we're being flexible, and you can have more room. But you can definitely do less. So yeah.

2:29

* Kresge 502 Cart: any other questions

2:53

* Kresge 502 Cart: cool. And then for the group part, hopefully, everyone has met with their teaching staff member and talked about your risk factor. But if you have any questions you can reach out to Michelle or I, and happy to chat

2:58

* Kresge 502 Cart: anything to add up about the assignment.

3:12

* Kresge 502 Cart: Then see, you guys, on Tuesday for your first group presentation. Awesome.

3:20

* Kresge 502 Cart: Alright yeah, slip should hit her head. She's fine, but she won't be in class today.

3:30

* Kresge 502 Cart: But there was a nice write-up. She did a nice interview of the Harvard Magazine, so I think we put an attachment on it.

3:42

* Kresge 502 Cart: Course websites react to one.

3:53

* Kresge 502 Cart: So that's a very nice thing to do. So it's my pleasure to introduce heather.

3:57

* Kresge 502 Cart: Heather has been really like a world leader in the epidemiology of breast cancer.

4:19

* Kresge 502 Cart: She's Pi, the principal investigator nurses, one and 2. So I had to lead credible cohorts, and she said, so much work, a lot of different areas, but a lot of it, hormones.

4:30

* Kresge 502 Cart: the etiology of breast cancer, but also a lot of depression options, carbon nutrition. So she really does really a world leader in this project. So we're really

4:50

* Kresge 502 Cart: pleased to have her get this talk

5:02

* Kresge 502 Cart: because you've been doing this at 5.

5:06

* Kresge 502 Cart: Something like that. Yeah, he took this course. Oh, yes, many, many years ago

5:08

* Kresge 502 Cart: I was, gonna say, Graham, but he talked cancer prevention desktop and then go full should work, or I can just share

5:19

* 6.

5:40

* Kresge 502 Cart: Okay, let me stop sharing. Just

5:41

* Okay?

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* Kresge 502 Cart: Oh, no. But you know what I did want to share my desktop, because

5:54

* Kresge 502 Cart: sorry

5:58

* Kresge 502 Cart: you'd think, after all these years of the pandemic, I would not have exactly what to do.

6:07

* Kresge 502 Cart: All right. So that's working on the screen working on. Zoom, I'm going to minimize this

6:14

* Kresge 502 Cart: perfect. Thank you. All right. Welcome, everybody. Nice to see you all here today and looking forward to talking a little bit about breast cancer today

6:24

* Kresge 502 Cart: and feel free to jump in with questions. I'm going to ask you some questions as we go along, and I would love to hear your thoughts as we're proceeding with this. So first, I'm going to start with a question for you.

6:39

* Kresge 502 Cart: So if you. Go to this QR code and I would love to hear you can put in just a risk factor for breast cancer that comes to mind for you.

6:55

* Kresge 502 Cart: And once you all have the QR code down, I'm going to switch screens here

7:07

* Kresge 502 Cart: when you get it.

7:22

* See a couple more phones up. Okay. So now I'm gonna see if I can swap over to

7:25

* that

7:31

* Kresge 502 Cart: this one awesome.

7:33

* Kresge 502 Cart: So I'm seeing Brca gene adaposity, obesity. childhood obesity, family history, mela parity

7:38

* Kresge 502 Cart: brackle, one genetic. Yeah. Age smoking. Calvi 2.

7:49

* Kresge 502 Cart: ATM,

7:56

* Kresge 502 Cart: yeah, definitely got some genetic focus on here. Great

7:58

* Kresge 502 Cart: family history. estrogen, postmenopause.

8:02

* Kresge 502 Cart: Great. All right. Well, we're going to talk about a lot of these today, and if we don't talk about them, and you have questions about any of these that you've put in, or that others have put in, feel free to bring it up. This is awesome, wonderful, thank you.

8:09

* Kresge 502 Cart: Great. So just as an overview, we'll go through a little bit of descriptive and epidemiology, and then go through risk factors thinking about how risk factors or breast cancer occur across the life course, focus, start on early life. Think about reproductive factors.

8:23

* Kresge 502 Cart: how endogenous hormones fits into this and underlies a lot of the risk factors risk factors that are modifiable or potentially modifiable, and then talk about mammographic density risk prediction. I actually took out because I didn't think we would have enough time as well as the subject. So sorry about that. I left those in the overview side by accident. So in terms of descriptive epidemiology.

8:39

* Kresge 502 Cart: I actually have another poll. So racial disparities in breast cancer exist, and which of the following best describes this disparity. So again, I'm going to swap screens, and I think you can still get the QR code if I go to the second question here.

9:03

* Kresge 502 Cart: So the it's a little hard to read here, but the options are the first one. Black and Hispanic women are more likely to be diagnosed with breast cancer than white women.

9:18

* Kresge 502 Cart: Second, one is black. Women are more likely to be diagnosed with breast cancer and to die of breast cancer than white women, the third, although white women have the highest incidence, rates of breast cancer. Black women have the highest mortality rates

9:28

* Kresge 502 Cart: the fourth black and Hispanic women have higher breast cancer mortality rates than white women. So see, see what you think about this.

9:41

* Kresge 502 Cart: and then we'll go through a bit of the descriptive epidemiology. So right now we have most people saying the third option. So although white women have highest incidence rates, black women have highest mortality rates, and a couple of people showing black and Hispanic women having higher breast cancer, mortality rates than white women.

9:50

* Kresge 502 Cart: others.

10:16

* Kresge 502 Cart: All right. So we'll go through some of the descriptive epidemiology and see what the answer to this question is.

10:19

* Flip back to Powerpoint here. Okay, so thinking about, I'm sure you are all familiar with global maps like this, looking at incidence of cancer across different countries around the world. And what you can see here is that the rates of breast cancer do vary quite a lot across different countries. And so what is something that you notice about this with a darker blue showing higher incidence, rates of breast cancer.

10:25

* Kresge 502 Cart: Sorry more towards the high income countries, high income countries. Right?

10:58

* Kresge 502 Cart: Yeah. And so, any ideas about what might contribute to that.

11:05

* Kresge 502 Cart: Why might we see this pattern

11:10

* Kresge 502 Cart: more screening? That's an interesting point. So more screening might be detecting more cases of breast cancer.

11:17

* Kresge 502 Cart: What else? What else might differ

11:26

* Kresge 502 Cart: obesity, obesity. So thinking about patterns of risk factors could differ across the countries as well as patterns of screening

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* Kresge 502 Cart: anything else.

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* Kresge 502 Cart: I mean.

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* Kresge 502 Cart: less developed countries

11:51

* question.

11:55

* Kresge 502 Cart: They die younger. You do other causes rather than developing cancer. Infectious causes.

11:55

* right? So potentially that shift between communicable diseases having a bigger impact and then noncommunicable diseases. Right? So but some of the things that you're all getting at are the fact that there are things other than genetics that differ. So there are different patterns or risk factors which leads me in in my interest in breast cancer. To think that maybe some of these differences are factors that are modifiable so that we can think about how to reduce rates of breast cancer and prevent breast cancer.

12:04

* Kresge 502 Cart: So the other factor that we can see plays into this. It really highlights that it's not all genetics being the difference. This is quite an old study, but it was really an interesting way of looking at how rates of breast cancer change with immigration. So, looking at the lowest.

12:34

* Kresge 502 Cart: her are Japanese in Japan, and then looking at Japanese immigrants in Hawaii and in San Francisco compared to the top, solid red being whites in San Francisco. And so you can see that as people move and spend more time in this country they end up adopting the rates of the higher incidence rates of the whites in the country, which again leads us to think that it's not genetics

12:53

* Kresge 502 Cart: that genes don't change this quickly, but it has to be something about the environment, lifestyle, or changes in reproductive patterns that could be contributing to these differences here.

13:18

* Kresge 502 Cart: So if we look at the age, standardized incidence rates across the world, you can see here the incidence and mortality this is ranked by instance. And again you can see patterns of the more

13:32

* Kresge 502 Cart: Westernized countries at the top with a higher incidence rates. But then, when we look and rank it by mortality rates, you can see a shift in countries. And so this is a pattern that is probably similar to looking at other cancers as well, that there's a difference in the mortality patterns across the globe.

13:49

* Kresge 502 Cart: So you can see when we look within the United States that breast cancer ranks as the highest incidence cancer, in the in females, and it is ranked second in terms of the number of cancer deaths that it causes and second only to the lung cancer here.

14:11

* Kresge 502 Cart: And then, if we look at the age incidence curve, there are a couple of of interesting facts factors here. One is that the age. Incidence incidence curve is quite steep in sort of early pre menopausal years, up to around the time of menopause, when the the rate actually flattens a little bit more after menopause

14:31

* Kresge 502 Cart: and then continues up, and you can see the differences by race and ethnicity here. So what can you see if we look at

14:55

* Kresge 502 Cart: non-hispanic black with the squares here versus non-hispanic white in the circles here. It's a little harder to see down at the bottom. But can somebody describe what they see here.

15:05

* Kresge 502 Cart: I would say that the rise in Hispanic white in the older age is a bit steeper than me.

15:36

* I'm just in that age group of like 60, 60 more, I mean the steep is higher.

15:44

* Kresge 502 Cart: right.

15:53

* Kresge 502 Cart: but in general it appears lower, altogether right, except for at the very bottom here, which again is a little bit hard to see. But it appears that at younger ages black women have a higher incidence of breast cancer

15:55

* Kresge 502 Cart: compared to white women, and in terms of looking at Hispanic of any race you can see, the curve here tends to be lower than both.

16:08

* Kresge 502 Cart: So, thinking about the question in the poll.

16:19

* Kresge 502 Cart: Okay? So then, if we look at trends over time, so on the left is what we call Dcis, so ductal carcinoma in site 2, which is considered stage 0. There is some controversy about whether we should call it carcinoma or not, and then invasive breast cancer. So stage one through 4 on the right, and if we look just at the black

16:26

* Kresge 502 Cart: bar here as anybody over age 20, and then the pink bars split it by younger ages, 20 to 49, and then 50 plus. And you can see some some differences here if we just focus on the invasive breast cancer curves to begin with.

16:52

* Kresge 502 Cart: what are the patterns, and what do you think might be contributing to some of the changes that we see over time?

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* Kresge 502 Cart: So, first of all, what are you seeing

17:19

* Kresge 502 Cart: just descriptively.

17:22

* age 56.

17:30

* Kresge 502 Cart: So you see an increase in the particularly in the 50 and older. Right? Yeah. And then what happens?

17:31

* Okay.

17:40

* yeah.

17:43

* Kresge 502 Cart: And then it decreases.

17:45

* Kresge 502 Cart: Yeah. So and then you see a similar, but perhaps even more sharp increase in the Dcis.

17:48

* Kresge 502 Cart: So what do you think could be contributing to this.

17:57

* Kresge 502 Cart: Not sure. What is that?

18:03

* Kresge 502 Cart: I'm still sharing a screen. That's weird. Okay.

18:09

* Kresge 502 Cart: there we go. No, I'm not still sharing the screen. Okay.

18:14

* Kresge 502 Cart: try again.

18:23

* Kresge 502 Cart: Okay.

18:32

* I'll try not to touch too many buttons. Ok, so what do you think could be contributing to this sharp increase that we saw in the eightys and early ninetys

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* sanctions.

18:47

* Kresge 502 Cart: lifestyle changes

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* Kresge 502 Cart: such as

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* Kresge 502 Cart: Hi, so you can certainly think about whether there are changes in lifestyle changes in the risk factors. And so you could think about smoking's not a huge risk factor for breast cancer rates have gone down in women in the Us. So that's probably not a contributor.

18:59

* Kresge 502 Cart: There is now standard screening and mammography for recommended

19:25

* Kresge 502 Cart: from the age of 50 or 40, but in certain population and high-risk populations, even younger, with other mortalities, screening

19:33

* Kresge 502 Cart: for about 50 years. Right? Right so. And this is a place where patterns of risk factors can change and obesity can contribute to this, but the really sharp increase is most likely due to screening. And in fact, this, this deeper increase in Dcis. These are very small tumors that are not easy to detect by lumps.

19:47

* Kresge 502 Cart: and so, but they are detected by screening mammography. So this is responsible for a lot of that increase in the incidence over time, and then it does tend to flatten out a bit. Anybody have any ideas? Why, we see a decline in about the early 2 thousands.

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* Kresge 502 Cart: Does anybody know anything about the Women's Health Initiative trial?

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* What was that? Yeah. The hormone replacement therapy that was found to be associated with that

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* Kresge 502 Cart: currently vascular races. So because

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* Kresge 502 Cart: practices were changed during that time. That's exactly right. So this, the results of the study was a long term trial of hormone therapy. In postmenopausal women, and as they published their initial findings with an increased risk of cardiovascular disease and an increased risk of breast cancer, thousands and thousands of women stopped taking hormone therapy, and it was in the early 2 thousands. And we can actually see that change in the breast cancer incidence.

21:04

* Kresge 502 Cart: And we'll go through hormone therapy in its relationship with breast cancer. But I think these curves, we tend to think, why is breast cancer increasing over time? But you can actually see increases and decreases related to particular events that were pretty widespread, both screening and this massive drop off in the use of hormone therapy. So it's kind of a fascinating way of looking at these.

21:32

* Kresge 502 Cart: All right. So breast cancer, we say breast cancer. But it's actually a very heterogeneous disease. And I think that this is probably something that you've talked about in relation to other cancers, or you will get to it in other cancers throughout the the course. And initially. One way of looking at this was by using gene expression and categorizing breast tumors by common gene expression patterns.

21:57

* Kresge 502 Cart: And what ended up being defined are these 4 or 5 different subtypes of breast cancer and the different subtypes have very different outcomes in terms of prognosis. So if we look at luminal A and luminal B. Those are the dark blue and light blue curves. So, and this is sort of an initial set, and then a validation set.

22:22

* Kresge 502 Cart: and then basal light, which are also similar to triple negative, which you may have heard about, and the herb, which is her 2 positive tumors, had a much worse prognosis, as you can see here and now, I will say that the her 2 positive tumors.

22:46

* Kresge 502 Cart: the prognosis for those, is actually a lot better now, because we have a targeted treatment for these tumors. So this is something that went from being a prognostic indicator of poor prognosis to becoming an indicator of a tumor that's going to respond to a very effective treatment. But nonetheless, it shows you that these molecular subtypes actually do have meaning in terms of what the natural history of

23:03

* Kresge 502 Cart: the disease and the outcomes could be. So this is established based on gene expression. When we try to classify tumors by their molecular subtypes and epidemiology studies for thousands of tumors. We don't have the resources to do gene expression on all of them, so we can classify them based on expression of a few different markers. So

23:28

* Kresge 502 Cart: estrogen receptor is one of the original classifiers of breast tumors, and whether there are estrogen receptors that are present in the breast tumor.

23:53

* Kresge 502 Cart: Those are er positive versus absent or er negative, and then within those we can use a few other markers to help us define luminal a and luminal B, which are both under the er positive, and they can either be her 2 negative and low grade, or her 2 positive or high grade. So these are all under er positive, and they get split a little bit into luminal A

24:04

* Kresge 502 Cart: in limital b, and then under the er negative, we have the her 2 enriched. So these, her 2 positive tumors, which I just mentioned, have this very effective targeted therapy, or the basal like, which are negative, for all of these markers, as well as being positive for 2 additional ck, 5, 6, and Bgfr

24:29

* Kresge 502 Cart: and then there's sort of this unclassified where they're negative for all 5 of these markers. And one of my colleagues at 1 point had said, I think they're just. They're they're positive for something. We just don't know what to look for yet in terms of subseting these tumors.

24:51

* Kresge 502 Cart: so when we think we can then lump them a little more. So, there are hormone receptor, positive tumors that are H negative or H 2 positive, and then her 2 overexpressing tumors. And then these triple negative tumors. So they're er negative Pr negative and her 2 negative. And I have the gray and pink dots here to help line up with what we're going to look at in the next side. So on the left side, this is looking at breast cancer, incidence and death.

25:09

* Kresge 502 Cart: By race and ethnicity. So if we're going to look at a white, black and Hispanic as the as I had in the poll. Question. First of all, what do you see for incidence rates in the light pink bars

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* Kresge 502 Cart: across these categories.

25:55

* Kresge 502 Cart: Why?

26:03

* Kresge 502 Cart: right? So higher incidents than the white women

26:07

* Kresge 502 Cart: black women are just a little bit lower. And hispanic women are lower than that, and then in dark pink are the mortality rates. So what what do you see here? So if we look at black versus white.

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* Kresge 502 Cart: In terms of mortality. What do we see?

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* Kresge 502 Cart: Right? So the mortality rates are higher in black women. Right? Yup. So that helps answer our question. And then, if we look at the on the right side, so this shows the distribution within these categories of race and ethnicity, the distribution of these molecular subtypes of breast cancer. And so if we again compare white versus black here, so the dark pink are the hormone receptors, tumors.

26:38

* Kresge 502 Cart: The light pink are the her 2 and hormone receptor positives. So those are sort of like the luminal, a luminal B, and then the light gray are the her 2 enriched tumors, and then the Darpa Gray are the triple negatives. And so, if you compare these distributions between white and black women, what do we see

27:05

* Kresge 502 Cart: but someone from this side of the room. What do we see?

27:42

* Kresge 502 Cart: Alright portion of the

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* Kresge 502 Cart: I'm sorry I really got vision, and I'm trying to read it. Hr. Negative for 2 negative

27:55

* right? So black women have a higher proportion of their breast. Tumors are these triple negative tumors.

28:01

* Kresge 502 Cart: and they have a worse prognosis. So triple-negative tumors. We don't have a very good target therapy for so the hormone receptor doesn't express an estrogen receptor. Negative

28:07

* Kresge 502 Cart: tumors are harder to treat, and they're more aggressive. So they have a worse prognosis. So some of this difference in mortality between black and white women could be contributed by the difference in the distribution of subtypes

28:32

* Kresge 502 Cart: and the other thing that that contributes to the difference in these subtypes is, if you think about the age incidence curve that we're looking at in younger women black women have higher incidence rates than white women, but then, in older women it reverses, and the

28:48

* Kresge 502 Cart: proportion of tumors that are triple negative tend to be higher in younger women. And so a lot of these patterns are going together, contributing to the difference in mortality rates. Now there are lots of potential differences in structural access to care, treatment, screening

29:08

* Kresge 502 Cart: all of these things can also be contributing to some of the disparities that we're observing between the mortality in white women and black women. But there are also some molecular differences that are adding to that as well

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* Kresge 502 Cart: any questions on this.

29:46

* Kresge 502 Cart: All right. So when we come back to the question, most of you picked the one that shows that although white women have the highest incidence rates for breast cancer, black women have the highest mortality rates, so it is racial disparities, but it shows up in a nuanced way in terms of the incidence and mortality

29:53

* Kresge 502 Cart: that's good when you adjust for the subtype.

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* Kresge 502 Cart: Yes, that's a great question, and yes, you can account for some of that difference by the molecular subtypes. But, as I was saying about structural differences in structural racism. There are differences in mortality that remain that are likely to do things that are not related to the molecular characteristics of the tumor.

30:20

* Kresge 502 Cart: Other questions.

30:47

* Kresge 502 Cart: alright, yes. it's good to see you nice to see you too.

30:51

* Kresge 502 Cart: first. But I was just wondering why black it's more than twice

31:01

* Kresge 502 Cart: right. It's a great question, and I don't think we have the whole answer for it. One of the reasons is that they tend to have more breast cancers at younger ages, and those tumors that develop are are slightly more likely to be triple negative tumors. Some of it could be related to the fact that we'll get into some of the reproductive factors. But after pregnancy, the the risk of breast cancer

31:12

* Kresge 502 Cart: increases for a window of 5 to 7 to 10 years after a pregnancy, and those tumors are slightly more likely to be triple negative tumors. So, seeing that, you know, increase the higher incidence rate in black women in younger ages they're gonna be more likely to be triple negatives which could be contributing to this.

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* Kresge 502 Cart: There may be other differences contributing it as well. But it's a good question.

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* Kresge 502 Cart: Other questions.

32:01

* Kresge 502 Cart: Alright.

32:06

* Kresge 502 Cart: so when we look at breast cancer survival, we've talked a little bit about it already. But one thing to note overall. What do you see from these?

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* Kresge 502 Cart: So this is looking at five-year survival in the left hand, ten-year and fifteen-year survival. So just looking at the five-year survival.

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* Kresge 502 Cart: you've probably talked about some other cancers in the class. What? What stands out to you about breast cancer?

32:25

* Kresge 502 Cart: What's that relative to 2 other cancers? There's higher.

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* Kresge 502 Cart: Yeah, yeah, so 5 years survival, 90% sounds pretty good. Right? It is pretty good. And it is different, you know. Compare that to something like pancreatic cancer, where you'd actually almost see the reverse of that. What do you see when you look at 5 year 10 year 15 year overall still pretty good. But what do you see?

32:37

* Kresge 502 Cart: Sorry

33:00

* Kresge 502 Cart: it decreases, it decreases. So with the tenure and the 15 year. And this is something that is a little more unique to breast cancer. So with colon cancer for women and men who survive 5 years, you're pretty much in the clear if you make it to 5 years.

33:01

* Kresge 502 Cart: have a good odds of much longer survival with breast cancer, there tend to be later recurrences, causing death, 10 to 15 to 20 years after the initial diagnosis of breast cancer

33:21

* Kresge 502 Cart: more unique to breast cancer. And it's a big question of why does this happen. And in fact, we talked a little bit about the fact that triple negative tumors have a worse prognosis. They're more aggressive. But there are a lot of er positives. So there's hormone receptor, positive tumors that can recur 10 to 15 to 20 years after that initial breast cancer diagnosis

33:37

* Kresge 502 Cart: and then ultimately cause breast cancer death. So that's something that is certainly a remaining question. To try to understand. Why is it that these tumors recur much later? And what can we do about it? How can we try to prevent some of those occurrences so

34:02

* Kresge 502 Cart: overall great survival rates, but still a lot to be figured out and potential places to intervene. If we can figure out how to do that.

34:18

* Kresge 502 Cart: is that

34:28

* Kresge 502 Cart: disease related deaths, or like, this is breast cancer, specific death? Yeah. Yeah. Good question. Right so. And and given that the overall breast cancer survival is very good. Most women who are diagnosed with breast cancer end up dying of another cause. But there is a significant breast cancer, death. As you go out.

34:29

* Kresge 502 Cart: So if we look at the survival rates by race.

34:55

* Kresge 502 Cart: you can see how it changed over time. So if we look overall at all races, you can see 5 year survival rates started at 75% in the up to 91% in the. And if we look at white versus black, you can see increases in both. However, at each time period they're lower for black women than for white women.

35:00

* Kresge 502 Cart: and I just wanted to show one other bit here in thinking about the disparities. So so this shows overall what we've looked at already. So this is 5 year survival rates for white women is 92% and 83% in black women. And we've looked already at the difference in molecular subtypes. And here you can look at the differences by

35:28

* Kresge 502 Cart: whether the tumor is localized or has spread regionally or more distantly. And you see these disparities at each stage. This does not account for molecular subtypes, but I think if you adjust for those molecular subtypes, you still see that there's a disparity in the survival between black women and white women.

35:52

* Kresge 502 Cart: Any questions?

36:16

* Kresge 502 Cart: All right. So that gets us through some of the descriptive epidemiology. Now we'll turn to getting into a little more detail in the risk factors. So I want to just give you an overview of the risk factors that are pretty well established at this point. So age we looked at the age, instance, for if you could see that it goes up, that's clearly a strong risk factor. Gender. We know that women

36:21

* Kresge 502 Cart: are much, much more likely to get breast cancer. Men do get breast cancer, but it is predominantly showing up in women. family history and genetics.

36:45

* Kresge 502 Cart: So some of you had put up Brca. One lb. 2 ATM. These are inherited mutations that carry a very high risk of breast cancer over lifetime. There are also genes that are more common snps that contribute a little bit to increasing risk of breast cancer. And you can think about. I don't know if you've talked about polygenic risk scores, but some of these more common mutations that

36:55

* Kresge 502 Cart: are associated with a slight increased risk can add up, so that if women have multiple markers they can end up with higher risk of breast cancer, benign breast disease is something that is now more commonly detected, thanks to mammography. And these are lesions that are not malignant. But they aren't changed.

37:20

* Kresge 502 Cart: They're from normal tissues. So they have hyperplasia, abnormal growth. That isn't cancer, but it increases a woman's risk of developing breast cancer. Later we'll get into endogenous hormones. So thinking about estrogens and androids that are naturally circulating in the body. Breastfeeding is associated with lower risk radiation. So when you have radiation to the chest increases, risk.

37:44

* Kresge 502 Cart: mammographic density which you can detect on a mammogram will go through exogenous hormones. We've already talked about hormone therapy, and we'll get into a little more detail alcohol, adipocy and physical activity. And so, as I noted. One of the pieces that you'll see here is that there are risk factors that occur across the life course. So we'll start with some of the earlier risk factors and think about

38:12

* Kresge 502 Cart: how they could be impacting risk of breast cancer decades later, and what that might mean.

38:37

* Kresge 502 Cart: So one of the things is thinking about windows of susceptibility. So when we think about changes in development over the life course, there are specific windows when there are really big physiologic changes that occur in the mammary gland. So you think about going through gestation, puberty, and then pregnancy and lactation. And so at each of these developmental stages there are chances that

38:44

* Kresge 502 Cart: risk factors could be having an impact on the development of the breast tissue on how breast tissue changes after pregnancy and lactation. Things like that. So this is sort of a conceptual model that was put together from a working group looking at environmental factors and their impact on breast cancer. But it's a good conceptual framework to think about the major phases

39:13

* Kresge 502 Cart: of life course development that parallel the development of carcinogenesis.

39:38

* Kresge 502 Cart: So as we go from prenatal early childhood, puberty, pregnancy, pre-menopause, postmenopause. You can think about changes in the breast tissue that could be happening along these same lines. So normal breast tissue progressing to hyperplasia, etc. And then the rainbow is representing the fact that etiologic factors could come into play at multiple levels of thinking

39:43

* Kresge 502 Cart: of the biology as well as behavioral and social levels that could be playing a role in these different windows of susceptibility.

40:08

* Kresge 502 Cart: So one of the really interesting pieces of evidence that suggests that

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* Kresge 502 Cart: childhood and puberty are a particular window of susceptibility, for breast cancer is actually looking at breast cancer rates in women who were exposed in Japan to the atomic bomb.

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* Kresge 502 Cart: And if you look at this, this is the age at which the the women were at the time of the bombing. So this is a very unique point in time exposure. And then looking across the life course after that, to understand the impact of that radiation exposure on the risk of breast cancer. And so you can see the relative excess risk. And so can somebody describe what you see here

40:42

* Kresge 502 Cart: incidents. if exposed to the

41:21

* Kresge 502 Cart: on if exposed, and I think your age is higher compared to people who are exposed to.

41:26

* Kresge 502 Cart: or laughter

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* Kresge 502 Cart: right? So it turns out that women who were exposed in their thirtys, fortys and fiftys had not much of an elevation of risk of breast cancer compared to the women who were exposed when they were children, or in their teens or twentys. So this really highlights for us that something really important is going on in the breast issue at that time, when the radiation exposure occurred in those younger ages.

41:36

* Kresge 502 Cart: You think about the radiation causing mutations that can then be carried on. They're impacting much more in the younger women in the younger breast tissue

42:00

* Kresge 502 Cart: sort of background evidence for us to think about. Okay? Well, what other exposures might be occurring in childhood and around puberty that could be impacting risk of breast cancer throughout the woman's life.

42:14

* Kresge 502 Cart: So one of the things that we're so let's see, several of you had put into the word cloud adaposity or childhood obesity. And so, looking at childhood weight is something that shows up as being a breast cancer risk factor, but potentially not in the direction you were thinking. So. The way we've gotten at this in several studies is by asking, women

42:27

* Kresge 502 Cart: call their body size or their body shape when they were different ages in childhood. So we use a pictogram like this, and ask the women to tell us what their body shape was like at age 5 and age 10, and we can use an average of that childhood, and then at age 20, and we can think about an average of 10 and 20 as being what they were like

42:52

* adolescents.

43:17

* Kresge 502 Cart: So this may seem like a fairly crude assessment of this, but it actually tracks pretty well with weight and bmi that were measured at age 18, where we can look at old records and compare that to the recalled body shape. And so it actually validates quite well. And what we see is the following. So if we look, this is looking at

43:18

* Kresge 502 Cart: average body size between ages 5 and 10. So thinking about this is childhood. And then this is the average scores from that pictogram. And this is in premenopausal women and in postmenopausal women. And so you can tell me what they see here.

43:45

* Kresge 502 Cart: Is this the direction you would have expected?

44:11

* Kresge 502 Cart: No.

44:16

* Kresge 502 Cart: let me see this.

44:23

* Kresge 502 Cart: the higher the it's not defined by these integrals. The higher the

44:25

* Kresge 502 Cart: rescue way that

44:34

* Kresge 502 Cart: the smaller the rate of breast cancer. And in premier puzzle women. It starts from the beginning, starts after the first to measurements or system.

44:38

* Kresge 502 Cart: So to me this is really striking, not only the inverse association, but the fact that it's something that lasts for many, many decades. So what a woman's body size was in in adolescence is impacting risk of breast cancer in her. In postmenopausal women. So really coming back to that windows of susceptibility. There's something going on at that moment that is potentially a set point. It's establishing something in the breast tissue that then gets carried on

44:59

* Kresge 502 Cart: throughout life. And it's really pretty striking, also a very hard message to think about with public health. This is not the message that we're thinking is the right thing to pass along.

45:29

* Kresge 502 Cart: So we also see it with both risk of er positive and er negative tumors. And so as we get a little further into thinking about adulthood adiposity. We'll see more of a difference between er positive and er negative but in this case childhood adiposity seems to be associated with lower risk of of both types of tumors.

45:41

* Kresge 502 Cart: So this was done in the nurses, health studies, but it has since been replicated in many other studies than many other populations. So, looking at a Japanese population, African, American, Scandinavian, all show this lower risk of breast cancer with higher weight at adolescence, child or adolescents. So it's really quite consistent

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* Kresge 502 Cart: over many, many studies

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* Kresge 502 Cart: question ready for biological explanation. Yeah, great question. I think later, I will show those same pictograms

46:31

* Kresge 502 Cart: with mammographic density. So we do see that it's associated with mammographic density. And so again, I think there's something about establishing. It's changing the breast tissue at that very early age and having some impact. But I think we're still missing a lot of those molecular pieces to really understand what's going on.

46:41

* Kresge 502 Cart: Yes, on the previous slide.

47:03

* Kresge 502 Cart: Oh, yeah. So this is taking the average of these numbers. Sorry, it's a good question. So we averaged between ages 5 and 10, and you'll note that you know, our highest category here is is 5 and a half plus. So it's really sort of lumping all of these larger sizes into that higher category. Yeah. Well, but no, it's a great question. It's not very well labeled here. So thank you.

47:10

* Kresge 502 Cart: great. Okay. So

47:35

* Kresge 502 Cart: then, age at monarchy is a pretty well established risk factor for breast cancer, and this shows decreasing risk with every year later that monarchy occurs. So this is when a woman starts having her menstrual cycle, and essentially the breast tissue is undergoing changes in development at that point.

47:39

* Kresge 502 Cart: And so here you see the longer monarchy, that initiation of Menzies is delayed, the lower the risk of breast cancer. Now, what do you make of the? If you look at

48:03

* Kresge 502 Cart: at this slide

48:16

* Kresge 502 Cart: versus this slide.

48:18

* Kresge 502 Cart: Did these? Did this make sense?

48:21

* Kresge 502 Cart: Does anybody know anything about adapting and monarchy, and how those go together?

48:25

* Kresge 502 Cart: Okay.

48:39

* Kresge 502 Cart: so do you know, if overweight, girls are more likely to have an earlier period or a later period when they first start.

48:47

* What's that earlier?

48:55

* Kresge 502 Cart: Right? So these 2 go a little bit at odds. They're not going in the same direction. And yet both of these are pretty strong. And.

48:58

* Kresge 502 Cart: you know, independent risk factors. So it is sort of fascinating to think about what's going on and trying to to disentangle this and we can see, you know, this is sort of thinking about this life course, exposure to estrogen. So the earlier monarchy starts the earlier you start on this you know, big curve of being exposed to estrogen estradial over the life course.

49:07

* Kresge 502 Cart: and then comes back down in menopause with menopause. So thinking about age, at monarchy. So one thing that has changed, you can see the Bmi in young adulthood is associated with. So this is the odds of having an earlier monarchy so higher. Bmi is associated with higher odds of having an early monarchy. So, just as you said.

49:31

* Kresge 502 Cart: overweight is usually associated with an earlier monarchy, and we can see that in this it's a big collaborative study that pulled together here in Japan

49:55

* Kresge 502 Cart: something like 40 50 studies. Oh, 117. I was way off. The other thing that's interesting is looking here. And what do you see in terms of year at birth.

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* Kresge 502 Cart: with odds of having an earlier monarchy?

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* Kresge 502 Cart: Exactly.

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* Kresge 502 Cart: it increased

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* Kresge 502 Cart: so at higher odds of earlier monarchy with later ages, later births, later birth, years. So later, birth cohorts. So over time, age at monarchy has been getting earlier and earlier. And so there are lots of factors that go into this. But if you look back at historical records, I mean, it's gone from an average age of 1716 to, you know, down

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* Kresge 502 Cart: 1211, and getting younger all the time.

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* Kresge 502 Cart: So we can then think about how things like this could impact risk of breast cancer over time. So these are things that are changing. This is a much slower change than perhaps the obesity epidemic, but it is nonetheless contributing to potential changes in breast cancer incidents

51:00

* Kresge 502 Cart: that we can look at as diet and lifestyle in childhood and try to understand whether those have an impact on agent monarchy and in the growing up today study, which is the children of the nurses, health study to participants. We've looked at a variety of different dietary factors, and I think Walter Willett was really assuming that it was going to be related to milk consumption, but found no relationship between milk, consumption, and adolescence

51:20

* Kresge 502 Cart: and onset of of monarchy, however, sugar sweetened beverages, so drinking lots of soda was associated with earlier onset of monarchy, so there are some shifts in our diet and lifestyle habits that are contributing to some of those shifts in monarchy as well, and probably lots of other aspects of the way our lives have changed, too.

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* Kresge 502 Cart: Any questions on this.

52:15

* Kresge 502 Cart: Was there a biological explanation, for

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* Kresge 502 Cart: we see childhood associated with?

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* Kresge 502 Cart: It's a good question, and you can think about the sort of pro insulinemic and very pro growth factor, aspect of adipoity and obesity could be contributing to some of those changes associated with earlier monarchy. There are probably other avenues and pathways that that are could be explored in terms of trying to understand that. But it is. It's an interesting one.

52:26

* Kresge 502 Cart: So this reduces the risk of breast cancer. It doesn't increase the risk of eating

52:58

* Kresge 502 Cart: grants and system

53:03

* Kresge 502 Cart: childhood adiposity. No agent! Oh, agent monarchy! So that's a good question. And I don't know that it's been picked up as a risk factor for other cancers.

53:05

* Kresge 502 Cart: I don't believe that it's related to ovarian cancer, at least not strongly.

53:19

* Kresge 502 Cart: Alright, so we'll keep going with reproductive factors and starting with pregnancy and age at first birth. So here this is from some breast cancer risk modeling that some of our colleagues have have done, and it shows 3 different incidents. Curves for hypothetical women who in the black line a woman who didn't have any children

53:30

* Kresge 502 Cart: in the red line. A woman who had one child starting at age 35, and in the green line a woman who had 4 children starting at age 20. And so what do you see here?

53:57

* Kresge 502 Cart: What would you say in terms of pregnancy and age at first birth, and how they impact breast cancer risk.

54:10

* Kresge 502 Cart: Yes, right? So, having a earlier age at first birth and and pregnancy becomes protective, then so you have a lower risk of breast cancer compared to women who don't have any births. And then, if you have a a child late in life, then that we call sort of the bump of increased risk after pregnancy

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* never quite comes back down. So those women have a higher risk of breast cancer compared to women who didn't have children, or compared to women who had children at an earlier age.

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* Kresge 502 Cart: pregnancies or just. I mean.

55:03

* Kresge 502 Cart: maybe, that those who had pregnancy at the younger age also had pregnancies. Right? Yes, you're right, you're right, and that's a good point. So tends to be women who have more pregnancies have a lower risk of breast cancer.

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* Kresge 502 Cart: But if the woman who had her first birth at age 35, and then had 2 more children, she still would be at an elevated risk of breast cancer compared to another person. It's a great point, though. Good question.

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* Kresge 502 Cart: all right. So we talked about those windows of susceptibility and what's going on in the breast tissue, and the breast tissue undergoes tremendous change with pregnancy and birth and lactation. And so you can think about a later age at first birth has more time between monarchy and the time of the birth, so that breast tissue develops.

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* Kresge 502 Cart: and then it undergoes these huge changes, and there's more chance for mutations to be accumulated in breast tissue, and then pregnancy throws all these hormones at the breast tissue, and can contribute to replicating some of those mutations that have been accumulated, whereas women who have a childbirth much earlier, that window between monarchy and childbirth is shorter, and fewer mutations would have had the chance to accumulate at that point

56:08

* Kresge 502 Cart: happens with the breast tissue physiologically, and then after birth and after lactation, the breast tissue undergoes pollution, and you end up with more differentiated cells in the breast tissue compared to women who haven't had children, and that actually helps protect against development of breast cancer.

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* Kresge 502 Cart: I did mention, though, that there is this window after a pregnancy where the risk of breast cancer increases. And so here you can see this is a large pooled analysis across many cohort studies where you can see the risk associated with

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* Kresge 502 Cart: the risk of breast cancer associated by time since most recent birth. So here you can see this spike, and it does take a while to come back down.

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* Kresge 502 Cart: Typically, we think about this window of susceptibility after a pregnancy as being sort of between 5 and 10 years. And again, think about those accumulated mutations having had this big flesh of hormones. That's a point that those mutations could be replicated and turned into a cancer at that point.

57:29

* Kresge 502 Cart: So the pregnancy and birth is sort of a tricky one in terms of thinking about the impact on breast cancer risk. So breastfeeding or lactation has shown pretty consistent evidence across many studies that breastfeeding is associated with a lower risk of breast cancer. And it does seem to be dose dependent.

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* Kresge 502 Cart: independent of parity. So if a woman breastfeeds has one child in breastfeeds for a very long time that accumulates that that benefit of lesbian. And recently there's been evidence that that suggests that this benefit is particularly notable in triple negative breast cancer. So Tnbc's triple negative breast cancer. And again, those are more likely to be diagnosed after pregnancy. So, having this benefit of breastfeeding

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* Kresge 502 Cart: on the breast tumors, particularly the triple negatives, it's a nice thing to be able to see.

58:42

* Kresge 502 Cart: So this is showing the lifetime duration of breastfeeding and risk of breast cancer. And again, this is from one of these large collaborative studies pooling the original data. It's not a meta analysis. It's actually pooling all of the original data and showing the lower risk of breast cancer with longer duration of breastfeeding. And this is accounting for the number of births that a woman had, too.

58:52

* Kresge 502 Cart: Questions on this.

59:17

* Kresge 502 Cart: All right. So age at menopause.

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* Kresge 502 Cart: Again. If you think about the Orange graph that I showed about that exposure to Estradiol and the earlier you go through Menarche, the earlier you start that large exposure to circulating estrogens, and on the other end of the spectrum age at Menopause.

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* Kresge 502 Cart: The later an age at menopause is, the more it stretches out that exposure to high levels of Estradiol. So a later age at menopause is associated with a higher risk of breast cancer. And you can see this particularly contrasting a woman who has a bilateral efrectomy. So both of her ovaries removed before the age of 45, has about half of the risk of a woman who goes through menopause

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* Kresge 502 Cart: after age 55. So it really does have quite a big impact in terms of thinking about ultimately the risk of breast cancer, and we can see it even looking at ages of natural menopause between age 50 and 55, as you can see here in the figure.

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* Kresge 502 Cart: questions on this

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* Kresge 502 Cart: alright.

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* Kresge 502 Cart: So thinking about the circulating hormones, we've done quite a bit of work trying to understand how. Oh, yes, go ahead

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* Kresge 502 Cart: for the check

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* Kresge 502 Cart: age at monarchy is associated with higher increases of breast cancer leader in life and early generations.

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* Kresge 502 Cart: But you see that early days

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* Kresge 502 Cart: so early monarchy is not associated with early menopause. It's just a question of you can have variation in both spectrum. So puberty at age 11 or age 15, for natural menopause, it's usually between 45, and 55. But it's usually independent of monarchy. So it's not a fixed amount of time

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* that the woman has.

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* Kresge 502 Cart: So if you think about again thinking about the exposures of estrogen. If you extend that on either end, because of earlier monarchy, or because of later menopause, you end up with an increased risk of breast cancer. But actually, if you think about it, the longer you have that reproductive span.

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* Kresge 502 Cart: whether it's by earlier menarchy and or major menopause that are highly risky breast cancer.

1:02:07

* Kresge 502 Cart: Yes.

1:02:17

* Kresge 502 Cart: I just had a few questions regarding women that can't have children. What is the difference in risk for that population. Good, really good question. And there's been a lot of interest in this

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* for women who have infertility and does the infertility impact breast cancer risk. And if women have infertility treatment, does that impact breast cancer risk? And there's been a lot of studies on this. And actually, nothing is showing up as being either terribly consistent or terribly strong in terms of it being a risk factor for breast cancer. But it does get you to wonder like biologically.

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* Kresge 502 Cart: Is there a hormonal link to the infertility. Could that be driving it in one way or the other? I think you can think about

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* Kresge 502 Cart: some women may, if you have polycystic, ovarian, ovarian, syndr, poly, cystic, ovary, syndrome. You tend to have higher androgen levels which are associated with higher risk of breast cancer, but it's not that consistent that we see, you know, infertility being associated with a higher or a lower risk of breast cancer?

1:03:01

* Kresge 502 Cart: Good question.

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* Kresge 502 Cart: And of course there are lots of different treatments for infertility, many of them hormonally related. So there's a lot of interest in it, but not a lot of evidence

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* Kresge 502 Cart: in a reassuring way, I should say there have been lots of studies, but nothing is showing it very consistently. Yes.

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* Kresge 502 Cart: and they have this. I understand that we can see this video related to Lower Lisbon breast cancer by apply the H. 2.

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* Kresge 502 Cart: The people who get after 35 is annually

1:04:02

* Kresge 502 Cart: breast cancer, you know to be. have any space. Do you have any experiences?

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* Kresge 502 Cart: Right? Right? So it is sort of thinking about this that you commonly think that women who have children have a lower risk of breast cancer than women who haven't had children. Pregnancy makes a difference because of what has been probably accumulated in breast issue up to age 35. That then gets replicated.

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* Kresge 502 Cart: Sort of terminal differentiation of the breast tissue happens so much later, after a late pregnancy that you end up with as actually being at a higher risk than Malibu.

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* Kresge 502 Cart: so many nuances in breast cancer. Yes, I'm not sure if there's data on this. But has there been a study looking at age of birth and 35 of the skin patients in it. The risk model here actually takes into account the spacing of the birth.

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* Kresge 502 Cart: And so there is some impact there that a woman who had a birth at 20 to 23 has a lower risk than a woman who had a birth at 20 and 35, but that 20 to 35 is still not as high as this

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* 35 year old, because she'd been through the pregnancy early at age 20.

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* Kresge 502 Cart: That make sense. Yeah, the good question.

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* Kresge 502 Cart: Bernie Rosner, who's a Biostatistician here, has done a lot of this modeling, and he came up with what he calls the birth index, which is a way of accounting for the age of pregnancies, the number and the spacing between the births. He has that all into one variable in the model, because the spacing does have an impact.

1:05:37

* Kresge 502 Cart: Other questions

1:06:01

* Kresge 502 Cart: alright. Okay. So we'll move on to endogenous hormones. So thinking about the hormones that are naturally circulating in our bodies, and there are a couple of ways that these can contribute to development of cancer. One is through proliferation. So hormones are acting as growth factors, and this increases opportunity for replicating a mutation that already exists in the tissue. So more cells

1:06:05

* Kresge 502 Cart: at risk of mutation occurring as well as promoting the growth of cells that have a mutation. After that initiation. There's also the possibility that estrogens could be contributing to cancer through genotoxic mechanisms. So estrogens get metabolized through hydroxylation.

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* Kresge 502 Cart: Yeah.

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* Kresge 502 Cart: so they can actually create atoms in the DNA and contribute to damaging the DNA and hypothesized to be genotoxic.

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* Kresge 502 Cart: So, thinking about again another way of thinking about cycling hormones. So we looked at the overall curve between before monarchy and then reproductive years, having a very high level of Estradiol. And then after menopause, and this looks at the monthly cycle and the variation in hormones, and you can see in the light blue bars. This is showing the mitotic rate of breast

1:07:03

* Kresge 502 Cart: cells, and you can see that it changes over the month of the period cycle, the menstrual cycle. So when estrogens and progesterones are high in the ludal phase, you can see that the mitotic rate, the rate of division of these cells in the breast. Epithelium is higher at that point. So this was a good hypothesis that these hormones are contributing to

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* Kresge 502 Cart: proliferation.

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* Kresge 502 Cart: So we've done a a number of studies. It's hard to look at Plasma Estradiol in pre-menopausal women. For exactly this reason, looking at the blue bar, depending on what day of the cycle. You measure it. You're gonna get very different estrogen item

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* Kresge 502 Cart: levels. So what we were able to do in the nurse's health study, too, is, ask women to collect samples that were timed in the menstrual cycle, so we asked them to collect them in the early follicular phase, when estrogens are pretty low, as well as in the mid-ludal phase, when estrogens are pretty high, and what we found was an increased risk with higher levels in the follicular phase. So in that sort of low end of the estrogen spectrum.

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* Kresge 502 Cart: and as we pooled our studies together with other studies of pre-monopausal circulating hormones. pretty,

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* Kresge 502 Cart: I would say, suggestive. It's still not really robust, but pooling together did show an increased risk of breast cancer with higher circulating levels of Estradiol. And this is looking at a range of normal in women. So women who tend to be on the higher range of normal for circulating estrogens have a higher risk of breast cancer.

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* Kresge 502 Cart: And then, in looking at Android, so circulating testosterone Andrine Dione, it is also fairly consistent across studies that higher levels in premenopausal women are associated with a higher risk of breast cancer.

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* Kresge 502 Cart: So we know in premenopausal women, most of the estrogen is produced in the ovaries which can then impact the breast tissue, as we can see in that mitotic rate. So after menopause.

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* Kresge 502 Cart: the ovaries no longer produce estrogens, but they keep producing androgens. So post monopausal women are still producing androgens, both from the ovaries and from the adrenal glands. And what happens is those androgens actually get converted into estrogens in the adipose tissue. So there are enzymes in the adipost tissue that can convert androgens into bioactive estradiol.

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* Kresge 502 Cart: So in postmenopausal women, those circulating estrogen levels which are much lower than they were in premenopausal women are are related to how much adipose tissue there is.

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* Kresge 502 Cart: So if you look at circulating estradiol levels among women across different Bmis, so different adiposity. You can see higher estrada levels in the overweight and obese women and lower estradiol levels in the Lemur women. So

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* Kresge 502 Cart: you can think about the

1:10:37

* Kresge 502 Cart: thinking about adiposity. We know that adiposity is contributing to circulating estrogens. So if we measure those hormones in postmenopausal women. And again, this is measuring a normal range of Estradiol. But women who are in the top

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* Kresge 502 Cart: 20 to 40% of those circulating levels are at a higher risk of breast cancer. So this is looking at a couple of different estrogen. So estridiol and estroan, sulphate as well as testosterone. So circulating androgen levels are also associated associated with higher risk in postmenopausal women.

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* Kresge 502 Cart: and one of the things I had looked at was whether the circulating hormone levels were still predictive of risk. If somebody had a higher risk of breast cancer based on their pregnancy, history, and their family history, and their history of benign breast disease. And we see that it's similarly predictive of higher risk, independent of some of these other risk factors.

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* Kresge 502 Cart: So any questions on the circulating hormones.

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* Kresge 502 Cart: So as we talked about, we'll get into a little bit of some of the modifiable factors. But you can think about how these relationships with the circulating hormones may be related to some of the factors that we're going to talk about. So we'll start with weight. And so here again from grand bullets. And Bernie Rosner, thinking about this, the modeling of risk between lean in the green dashed line, average weight in the red and then obese in the blue.

1:11:51

* Kresge 502 Cart: Tell me what you see here.

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* Kresge 502 Cart: Yes, just to understand. Oh.

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* Kresge 502 Cart: one is that the graph? Just question whether the lean average weight in obese was it defined? At what age was it at younger age, or at the time of diagnosis across the life course.

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* Kresge 502 Cart: Average weight orderly. That's a good question. And you're just going to say it has a much higher incidence of obese persons as they learn

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* Kresge 502 Cart: right. But what happens early? What do you see early

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* Kresge 502 Cart: in the last 2?

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* Kresge 502 Cart: But it's, in fact, on the low end that occurs. So just as we talked about childhood adipocy contributing to a lower risk of breast cancer. Here you can see that adiposity throughout the reproductive years is associated with a lower risk of breast cancer, too.

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* Kresge 502 Cart: Excuse me, swallowed my water round.

1:13:29

* Kresge 502 Cart: and then these lean women, who we know, if you're lean as a child, you're at an increased risk of breast cancer. But after you reach menopause, you end up benefiting from being lean. Right? So we can think about. As a woman enters menopause. The adipose tissue that she's carrying is contributing to those circulating hormones. So you end up seeing a higher risk of breast cancer in the obese woman and the lean women end up, then switching to having a lower risk of breast cancer.

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* Kresge 502 Cart: But this is one of these. This is one of those hard to think about in terms of public health messaging. It's great to be overweight in terms of breast cancer risk before menopause. But then it's bad after menopause, and also, by the way, it's not great for other chronic diseases. So

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* Kresge 502 Cart: it's a hard one to think about. But this is very, very consistent. So I wanted to show you. This is a more recent pooled analysis that pulls together many, many studies, including our health study and nurses. Health study, too.

1:14:18

* Kresge 502 Cart: So this is looking at Bmi between 35, and 44. So we already looked at childhood. And now we're looking sort of the middle of those reproductive years. And you can see this very consistent dose response relationship between increasing Bmi at these ages and lower risk of breast cancer. And

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* Kresge 502 Cart: you know, some of this could be well were they overweight as a child, and maybe they got the benefit then. But even when we adjust for childhood out of posterity, we still see this relationship, that it's an inverse association with breast cancer risk.

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* Kresge 502 Cart: But then it changes again as we saw in that first curve, it changes with menopause. So looking at

1:15:08

* Kresge 502 Cart: overweight after menopause. So this is looking at weight change since age 18. And Bmi, we know, is not the greatest measure it gets at out of posterity. But if you think about weight change since age 18 in most people, and weight that is gained is adipose is adiposity sort of across the life force. So we can see here that women who gain weight have a have a higher risk of breast cancer

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* Kresge 502 Cart: after menopause. And this is among non-hormone therapy users, because again, we know that adiposity contributes to circulating estrogen levels.

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* Kresge 502 Cart: And if you add in hormone therapy, you're already adding lots of exogenous hormones which is going to increase your risk. So you can most clearly see the association between adiposity and breast cancer in women who are not taking hormone therapy, and we see this coming back to the er status of the tumor, we see an increased risk with weight gain for the er positive tumors that are fueled by estrogens.

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* Kresge 502 Cart: and we don't see much of an association at all with er negative tumors that are not fueled by estrogens. So this suggests to us that adiposity is contributing to risk likely through a hormonal pathway.

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* Kresge 502 Cart: So one of the things that I was interested in was was, well, if women can lose weight, does that lower their risk of breast cancer? And, as you can imagine, it's very hard to study women who have lost weight and chucked it off. For a long time. We had to wait a long time in the nurse's cell study to be able to do this analysis. But we see that women who lose weight after menopause

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* Kresge 502 Cart: are at a lower risk of breast cancer, and in the dark blue bars there are people who lost the weight and were able to keep it off. And interestingly, in a lot of studies. We've seen this again in a large pooled analysis as well, and it doesn't seem to matter why women lost weight, so you can think about was the weight, loss, intentional or non intentional.

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* Kresge 502 Cart: But, in fact, your adipose tissue and those circulating estradiol levels. It doesn't matter whether it's intentional or not intentional. It is contributing to lower estrogen levels overall

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* Kresge 502 Cart: any questions on that on out of custody.

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* Kresge 502 Cart: All right. So hormone therapy. I'm going to remind you about the incidence curves over time, and how we saw that decline in the curve after the publication of the Women's Health Initiative. So in our studies we see and had seen long before the Women's Health Initiative was published an increased risk of breast cancer with use of men, pausal, hormone therapy, and it increases with longer duration.

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* Kresge 502 Cart: Use so estrogen plus progestin for less than 5 years, and then this is estrogen plus proges. For more than 5 years

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* Kresge 502 Cart: now we do see in our cohorts an increased risk with estrogen alone, whereas women's health initiative, actually saw an inverse association. There are a lot of differences between the randomized trial and observational studies, one of which is the women in Women's Health initiatives started taking hormones

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* Kresge 502 Cart: many years after the onset of menopause, which is not typically how women take them now, or had taken them previously, so that could have contributed could be chance one way or the other. But it is a difference between the randomized trials and the observational study. But the plus P. So the estrogen plus proges is very consistent.

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* Kresge 502 Cart: And then you can see here this is again this large pool of analysis, looking at estrogen plus progestin, and going up to a 2 and a half fold increased risk for women who've taken it for more than 15 years of use.

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* Kresge 502 Cart: and then past users. So once women go off hormones, as we saw in that decline in the incidence of breast cancer over time, they have a lower risk of breast cancer compared to women who are current users.

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* Kresge 502 Cart: So you can think about it as you go off hormone therapy, and it sort of puts the brakes on whatever in terms of growth, being fueled by those hormones.

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* Kresge 502 Cart: So, and then thinking, putting together the hormone therapy and the adiposity. This is sort of a nice figure looking at the incidence of breast cancer. Among this is across Bmi, so different categories of Bmi and looking at estrogen and progestin use so exogenous hormone therapy, estrogen only. So this sees a a difference, but still an increased risk.

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* Kresge 502 Cart: The way we had seen in estrogen only, and then this is among never users looking at the across Bmi, so you can see an increased risk of breast cancer with higher Bmi. And then this splits it out by whether it was er positive tumors or er negative tumors, and you don't see much difference

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* Kresge 502 Cart: for er negative tumors. But you do for er positive. So I like this because it sort of puts into the same figure what the impact is of endogenous circulating hormones from higher Bmi versus adding, exogenous hormone therapy and looking at the impact on breast cancer?

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* Kresge 502 Cart: All right. Questions there.

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* Kresge 502 Cart: Yes. just the

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* Kresge 502 Cart: to the presence of prisons. Vary on. If it's brca, one or 20, great question. It does so. Brca, one tumors, I think, are more likely to be brca, one vary.

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* Kresge 502 Cart: Yes. Yeah. Good question. Yeah.

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* Kresge 502 Cart: Alright, so we'd already seen the impact. I just wanted to show you this is looking at the seer data from California, where you can see again this big drop off in breast cancer incidence.

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* Kresge 502 Cart: right after the self initiative was published, and all these women stopped taking hormones. So I always think it's epidemiologically kind of neat that you can see the impact of a pretty wide population level change in a risk factor.

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* Kresge 502 Cart: Okay? So again, showing you the exposure to Estradiol over the lifetime weight adds after menopause, and then thinking about hormone therapy, and how much that adds. So just thinking biologically, what's going on with hormones.

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* Kresge 502 Cart: alright oral contraceptives are associated with an increased risk of breast cancer. But oral contraceptives tend to be taken by younger women who are at lower, absolute risk of breast cancer. And so and then, after people stop using the risk declines so that there's 10 years after stopping oral contraceptives, there's no increased risk

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* Kresge 502 Cart: of breast cancer.

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* Kresge 502 Cart: Okay, so I'm gonna try to go through some of these next few slides a little quickly. So we I can spend some time on the mammographic density. So alcohol is a very consistent modest but consistent risk factor for breast cancer. And you can see it, even at pretty modest drinking levels, that there's a significant increased risk of breast cancer. And it seems to be for both er and er negative tumors.

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* Kresge 502 Cart: Carotenoids are the colorful fruits and vegetables that are high in Alpha Keratin and Beta Carotene we can see a lower risk of breast cancer among women who have higher circulating levels of carotoid. So we can measure this in the blood about a 15 to 20% reduction in breast cancer risk

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* Kresge 502 Cart: for women in the top. Fifth, compared to the bottom. Fifth. And here we see the opposite of atop. We actually see a stronger association between carotenoids and er negative breast cancer. So it seems like they are more beneficial for preventing these more aggressive, harder to treat tumors. So this is a highlight. I like that. We could all stand to eat more fruits and vegetables, and it could benefit breast cancer, risk as well.

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* Kresge 502 Cart: Physical activity, modest but pretty consistent, associated with a lower risk of breast cancer more convincing

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* Kresge 502 Cart: were consistent among postmenopausal. But it does seem to impact both, and Iarch did conclude that there was convincing evidence that it reduced risk of breast cancer, and we can see it in our cohorts. And one of the things again that I'm interested in is there a message we can say it's never too late to modify your behaviors that could impact, risk. And so we looked at whether women who change physical activity after menopause

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* Kresge 502 Cart: could change or had a lower risk of breast cancer. And we did see women who were not very physically active before menopause, but became physically active after menopause had a lower risk of breast cancer compared to women who were consistently low physical activity.

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* Kresge 502 Cart: So here's sort of a summary of thinking about the impact of modifiable factors. So the mean incidence rate in the population is here. When we look at single factors, if we set population levels to the lower risk for weight change. So adiposity, menopausal, hormone, therapy, alcohol, physical activity and breastfeeding. We can see the impact that this would have on incidence. And

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* Kresge 502 Cart: and when we put it all together. It has a pretty substantial impact on the incidence of breast cancer. So nice again to think about, are there ways we can modify lifestyle diet things like hormone therapy that can reduce the risk of breast cancer.

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* Kresge 502 Cart: Okay? So mammographic density well established, positive association between mammographic density and breast cancer risks. And this shows there's legislation now that requires women to be informed whether they have dense breasts on a mammogram.

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* Kresge 502 Cart: So this shows you going from a gradient of very fatty breast tissue to very dense breast tissue, and how it shows up on a mammogram, and underneath it shows the relative risk associated with these categories. So it's pretty striking a fivefold increased risk for women who are in the top quartile of density compared to women in the bottom, having no breast density.

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* Kresge 502 Cart: And so one question is, well, what you know what's going on here, and one aspect of it is, you know, could it be that

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* Kresge 502 Cart: dense breasts are much harder to find a tumor in compared to fatty breast tissue, and if you look at the time from mammogram to diagnosis, you see that there is a higher relative risk in that earlier time period, but that then, you know, the risk continues so you could think about. You know many of the cases that are diagnosed

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* Kresge 502 Cart: within a year or 2 after a mammogram. It could be that the breast density is a masking the tumor, and that it's hard to detect. But the fact that 10 years later women who, with dense breasts have a higher risk of breast cancer suggests that the breast density is showing us something about risk. It's not just

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* Kresge 502 Cart: masking an existing tumor is the use of ultrasound and MRI chained.

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* Kresge 502 Cart: I mean, this is from 95. Yet. Now we use multiplied for these.

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* Yes.

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* Kresge 502 Cart: right? So that's a good question. So maybe this is actually lower, because we're detecting them better if they get moved on to the next step. And that's a great question. I actually don't know that it's possible. But my guess is that there's still some that are gonna be hard to detect.

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* Kresge 502 Cart: So this is with er status. We see a mammographic density associated with both er negative and er positive. And remember, I was. Gonna I mentioned this that we see again these measures of adiposity in childhood. With the average over age 5 to 10, so that the women who were more overweight as children

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* Kresge 502 Cart: have lower mammographic density much later in life. So clearly, I mean that to me points to something happening at the level of the breast tissue early on in life. That's kind of a set point creating a difference in that breast tissue, and we can see that the

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* Kresge 502 Cart: association between childhood adiposity and breast cancer risk is mediated somewhat by mammographic density. So it's like between 30 and 50% whether it's Premenopausal or postmenopausal women. So some of that relationship between adiposity and breast cancer risk, we're picking up through a mammographic density relationship.

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* Kresge 502 Cart: any questions on that.

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* Kresge 502 Cart: So I will say one other thing that's pretty cool about mammograms today is

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* Kresge 502 Cart: clinically, they're categorized in density. But you can imagine that maybe with AI there could be lots more information in this image. And so we've been working with some colleagues at Mit and at Mass general who are using AI tools to develop or to get more information out of the mammogram beyond

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* Kresge 502 Cart: demographic density. So, reading the pixels at a much finer level and finding that there is more information about breast cancer risk. Biologically, we're not understanding it yet. But I think there's more to be gleaned there.

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* Kresge 502 Cart: Okay, so I have one final menti, and that is, can you name a breast cancer risk factor that was new to you today?

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* Kresge 502 Cart: And I'll switch over to the final question here.

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* Kresge 502 Cart: Are there anything that you had not heard about

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* Kresge 502 Cart: adipasty. It's an interesting one, isn't it? Not so straightforward in breast cancer.

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* agent, monarchy, great.

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* Kresge 502 Cart: Another audacity. Lower Bmi. In early life. Yeah.

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* Kresge 502 Cart: Monarchy.

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* Kresge 502 Cart: obesity

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* Kresge 502 Cart: great. So it sounds to me like, maybe you had heard about some of the reproductive factors being associated with breast cancer, risk, and hormone therapy, perhaps but thinking about what's going on early in life is is new for a lot of you, and it's pretty fascinating, and I wish we had better answers to try to tease it apart. But I'll leave that. I'm happy to say. If people have questions and thanks for your attention and your contributions.