* Kresge 502 Cart: We have. Unfortunately, I think, Covid and other respiratory infections running rampant. And so we have people who are going to be joining. I hope you all stay healthy and tough times.

0:12

* Kresge 502 Cart: We've always gotten struck with all sorts of things in this class. So before we get started, and we have an amazing guest lecture. Today, we're gonna start out with our usual cancer epitia. Today's question is which of the following cancers has the lowest estimate of heritability. And if you remember, heritability is the relative contribution of inherited

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* Kresge 502 Cart: genetic factors to the incidence of cancer. Is it a noma B prostate cancer, c, testicular cancer or D colon cancer. So which one has the lowest estimate of heritability

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* Kresge 502 Cart: of the lowest, relevant genetic fibers

1:08

* say.

1:28

* Okay.

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* Kresge 502 Cart: do you know the answer? No

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* Kresge 502 Cart: melanoma's in the clear lead right now.

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* Some of them voted for testicular cancer.

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* Kresge 502 Cart: Testicular cancer is a fascinating cancer. I don't think, unfortunately, anyone signed up for it for the project. But it's a really interesting cancer. All right, let's give it about 10 more seconds

1:53

* Kresge 502 Cart: and 5 more seconds, 3,

2:07

* Kresge 502 Cart: 2, and one great so the the melanoma and prostate cancer actually are tied for the 2 cancers that have the highest estimate variability. I know we haven't had our prostate cancer lecture yet, but they're the 2 cancers that seem to have the strongest genetic contribution based on family based studies and twin studies, which is quite interesting. Conrad stops up when he lectures. We'll talk about prostate cancer. Melanoma is interesting.

2:13

* Kresge 502 Cart: and I think part of that heritability or in her genetic factor around things like genes that put people at different predisposition to sun exposure, probably, I think, but there may be other genetic variants as well in the moderate level. It actually has a really strong family history.

2:46

* Kresge 502 Cart: A person has a brother or a father who had cicular cancer. Their own risk of Cisco cancer is substantially elevated. About half of that family history is actually due to some shared environmental factors. Interestingly, so, it's an interesting cancer that way that a lot of times we think of family history as being such a strong genetic susceptibility. But into circular cancer, the family history, a big chunk of

3:11

* Kresge 502 Cart: is actually due to shared environmental factors and then genetics. And then so colon cancer ends up being the cancer with the lowest estimate of heritability.

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* Kresge 502 Cart: Probably the 10 major cancers. I think so Colon and rectal cancer together. Step one. Cancer also has a relatively low estimate of heritability. So great, excellent! Introduce.

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* Kresge 502 Cart: Don't say too much.

4:02

* Yeah. Yeah.

4:27

* Kresge 502 Cart: I was lucky to get me young as my student he was a great, great student, but now he's already he's progressed rapidly. He was

4:34

* Kresge 502 Cart: like after he, when did you graduate? 2050? Nk, yeah. So then he was at the went to Mgh. Mass. General hospital, but also has connection to school public health, as you can clearly see there. And last last year he was promoted to associate Professor. So he's obviously doing. Great. He he's

4:43

* Kresge 502 Cart: does a lot of work on colorectal cancer. And he has, like broad base knowledge and like microbiome metabolomics, basic epidemiology.

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* Kresge 502 Cart: and does other things besides colorectal cancer. But that's one of his primary areas. And I used to give this lecture. And then few years ago, he started taking over. We was getting better comments better. So I said, Okay, you have to stop giving the lecture. So

5:21

* Kresge 502 Cart: thank you. Thank you. Introduction now. So it's really my great pleasure to be here. I remember the last time I was in this classroom, I mean as a student was actually for the cancer epic class speaking when Dimitri was giving the liver cancer. Yeah, it was one of the most impressive lectures that I have ever taken.

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* Kresge 502 Cart: So it's great to be back to this class. And as I mentioned, I've been lecturing for the class for a few years. I learned something new. Actually, I just learned something new from the question. It's actually good, because I was deciding to cut.

6:05

* Kresge 502 Cart: although last year as well. So I actually covered a genetic lecture because the genetic variance that we have identified seem to have pretty modest situation with colon cancer. That also makes sense that colon cancer is at least heritable among the major ones. So anyway, let's get started.

6:29

* Kresge 502 Cart: This is outline for today's talk. I first want to briefly talk about the descriptive epidemiology of Colorado cancer. So this is the most updated data from the American Cancer Society regarding new cancer cases and death phase in this country, as we can see here.

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* Kresge 502 Cart: we can see here colorectal cancer ranks. The third in both men and women, and also for both incidents and mentality. And it comes for about 8 to 9% of deaths among all cancers. So it's definitely still a major cancer in this country.

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* Kresge 502 Cart: So this shows the trend of coronal cancer, incidence and mortality in the United States. In the past few decades, as we can see, luckily both incidence and mortality have been declining. So this is encouraging. However, as we can see here, the reduction in mortality is

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* Kresge 502 Cart: much slower than that, for instance. So, as you may have learned from Epqer one, so that leads to higher prevalence, that means there is a growing number of individuals living with colon cancer in the country. So in the most recent report, there is about 1.1 million Americans living with cancer in 2,016, which represents a 20% increase compared to

7:58

* Kresge 502 Cart: so addressing the increasing number of the staff efforts is a huge is a huge concern in the cancer research community, especially for colon cancer. And I will touch on that later. So regarding the reasons for the decline for both incidence and mortality in this country. So this is a result based on the simulation analysis

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* Kresge 502 Cart: processes from a calorie risk from 1,975 to 2,000. So it's a little bit old, but still I think the numbers probably still holds, as we can see here, according to the model estimates.

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* Kresge 502 Cart: Now, 53% of the reduction is likely due to screening. So colonoscopy screening has been increasingly used in the country, and the screening uptake has been gradually growing as well, so we'll talk more about that later and risk factor. Improvement also accounts for about 35% of the decline, and this is mainly driven by the reduction in smoking

9:06

* Kresge 502 Cart: and also other unhealthy lifestyle. And there's also additional contribution of treatment about 12%. So this is from epneuric data. And if you know about economic analysis. Actually, the treatment actually consumes the largest of

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* Kresge 502 Cart: the economic burden for colon cancer. But compared to the risk factor and the screening, it actually contributes the least. So this highlights the importance of prevention.

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* Kresge 502 Cart: And interestingly, for colon cancer among young individuals below age 50, there is a growing increase, as you can see here for the older individuals, for age 40 to 64, and for about 65, there has been a decline. But for young individuals

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* Kresge 502 Cart: there has been an increase since, as you can see here, this patent holds for both men and women, and you probably have read from the news like from the press. There is a huge, a lot of discussion about what is driving this increase. The answer is, we still don't know. And this is a big question to be addressed.

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* Kresge 502 Cart: And interestingly, it's not just like America. It's across the globe, even for some middle or low income countries. There is also an increase in early onset colored cancer, and specifically in this country some notable demographic differences.

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* So it seems like the instance of early onset called a retro cancer, which is defined as cancers

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* Kresge 502 Cart: diagnosed among individuals aged 50 or younger. So it has been stable among blacks and Hispanics, but there has been a substantial increase in non Hispanic whites, and also it varies by state, and the increase is most predominant in Western States, such as Washington and Colorado.

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* Kresge 502 Cart: Very interesting talent can I say, yes, is it? Was it because of those rates were already lower? And so they had more growth to grow? Or is it something else? Yeah, that's part of the reason, because, like the Western States tend to have lower rates in general as a southern stage, have much higher rates. Yeah.

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* Kresge 502 Cart: yeah, I think it's very interesting for Colorado, I remember from the obesity IP like it has the lowest obesity. So it's interesting.

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* Kresge 502 Cart: And here I really want to highlight. It's not just the age. It's actually also a birth cohort effect. So this is a figure from a recent review on this topic. It shows that in this ratios of Colardo cancer by birth cohort across different regions in the world, using the birth cohort of 1,950 as a reference.

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* Kresge 502 Cart: As we can see here across all regions there has been an increase after the 1,950 birth cohort.

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* Kresge 502 Cart: and here the increase is actually most dramatic for East Asia.

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* Kresge 502 Cart: And if we look at the age and birth cohort effect together, this is data from again from the United States, from the American Cancer Society. So the X axis is a birth cohort, and the different color represent different age groups.

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* Kresge 502 Cart: as we can see, still, like after age. First of all, I want to measure this is 50 to 54 group. So we can see there's also a slight increase

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* Kresge 502 Cart: for the older, for the more recent birth cohort compared to the older, like birth cohort. So again, it seems like it's not just the age. So there has been some projection that over time as the new birth cohort ages. We will also see an increasing instance of

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* Kresge 502 Cart: Colorado cancer even among older individuals.

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* Kresge 502 Cart: And again, we can see there seems to be an increase after the birth cohort. So I really want to put this out, because I know there has been a lot of discussion, a lot of coverage on early onset cholesterol cancer. But as an epidemiologist, I hope you can understand. It's not just the age. It's really a birth cohort, in fact.

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* Kresge 502 Cart: so especially because screening is normally recommended for individuals at age 50. So the screening has kind of cut a lot of the older onset of colorectal cancer. But still over time, we still see a growing increase, a green increase in colorectal cancer

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* Kresge 502 Cart: across age groups are for the more recent birth cooper.

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* Kresge 502 Cart: So this, this epidemiology data seems to suggest that there must be something related to the birth cohort like to the environmental changes over the more recent birth cohorts. So here are the like

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* Kresge 502 Cart: possible reasons that have been proposed in the literature, including unhealthy lifestyles, such as obesity, Western diet, and lifestyle, and also there is a strong interest in studying early life exposures. This is particularly relevant to early onset cholera, because for younger individuals their exposure history is much shorter, and the critical period, maybe.

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* Kresge 502 Cart: is more likely to be in the early life period compared to older onset cancers and also the environmental change. We know that the environment has changed dramatically over the past few decades. So air pollution and climate change related climate change issues that may also play a role. And also I'll talk more about the microbes later. It can be

16:02

* Kresge 502 Cart: considered as a marker of the environmental change, because macrobound is very responsive to the environment, and any changes in the environment can be imprinted in the microbound. So by studying macrobound, we can get a lot of information about the environmental exposures.

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* Kresge 502 Cart: Any questions so far.

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* Kresge 502 Cart: Ok, oh, yeah. So you just mentioned that I can cover environmental changes. I was just wondering to what extent

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* Kresge 502 Cart: I know there's a lot of talk to them being exposed to just food. Yeah, yeah, that's a good question.

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* Kresge 502 Cart: I will talk more about this later. That for microbound, our understanding is still very premature. It's still a green area. But I think, like the more we study, the more we realize, like how individualized macrobound is. So that really suggests that it's the totality of the environment that really shapes the microbiome. I mainly focus on the gut microbound.

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* Kresge 502 Cart: and there has been very compelling data really indicates that a variety of exposures that lifestyle medication, environmental exposures can all influence the microbes. And if we look at each individual factor, the impact is very small. So that's another tricky thing with microbes effective for individual

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* Kresge 502 Cart: factors is very small. It's the totality of the environment that really shapes the.

18:09

* Kresge 502 Cart: So next, I want to briefly talk about the molecular features and the natural history of colorectal cancer. So among all cancers, colon cancer is probably the best characterized cancer molecular. So there are 2 major pathways for the development of polaroidal cancer. One is the chromosome or instability Pathway.

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* Kresge 502 Cart: which is characterized by multi-step genetic mutations. It starts with Apc. And then Kras and smite 4, and also PP. 53. And there is an increase in the chromosome instability over the natural history

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* Kresge 502 Cart: is the microsatellite instability. So the 2 pathways are very different molecular. So the macrosatellite instability pathway is characterized by the activation of the DNA may match repair genes.

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* Kresge 502 Cart: and also the related hypermethylation. So cancers developing through this pathway is characterized by microsatellite instability and also hypermethylation.

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* And for colon cancer.

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* Kresge 502 Cart: The natural history evolves from normal epithelium to adenoma and then to cancer. And these 2 different pathways also contribute to histologically different praker solutions, like different adenomas like for the microsatellite instability pathway, it is underlying the development of the surveillance

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* Kresge 502 Cart: of the years to be called a serenity Adenomas, and which is very different from conventional adenoma which develops through the chromosomal instability pathway. So

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* Kresge 502 Cart: again, it really highlights the heterogeneity of Colorado cancer.

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* Kresge 502 Cart: not just molecular, but also risk of actor wise. We will see that later.

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* Kresge 502 Cart: Yeah. So the microsatellite instability pathway is also called a serrated pathway, because it's characterized by the precursor illusion, serrated columns.

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* Kresge 502 Cart: So next, I want to spend some time going through the different provision strategies, and also by talking about the risk factors for colorectal. As an epidemiologist, this is probably the most important and the most interesting to us.

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* Kresge 502 Cart: So for primary prevention, as you must have learned, it's about prevent cancer from occurring.

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* Kresge 502 Cart: So here for the risk factors, we have been focusing on diet lifestyle and medications.

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* Kresge 502 Cart: So here is a summary of the factors that have been shown to increase risk of colorectal cancer.

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* Kresge 502 Cart: including smoking alcohol obesity, sedatory lifestyle. Red are processed meats and Western diet in general.

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* Kresge 502 Cart: So before I go over the individual risk factor, I just want to show this study. This was the study I did during my final year of the Phd with Ed, so we look at the potential

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* Kresge 502 Cart: preventability of cancer, including collateral cancer by lifestyle modifications. So we considered the 4 major lifestyle factors, including smoking alcohol obesity and physical inactivity, and we calculated the population attributable risk by comparing the high risk group versus a Low Risk group. So the Low Risk group is defined by

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* Kresge 502 Cart: a combination of all these 4 different different, like

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* Kresge 502 Cart: risk factors. And we can see here in our nurses, health study and health professional phlog study. We found about a 20 to 30% difference in terms of the incidence of collateral cancer in men and women, and we know that the nurses and Hpfs, as you probably have learned from this class or other class. It's

22:29

* Kresge 502 Cart: the participants are all health professionals, so they tend to have healthier lifestyle. So we also compare our population to the US. General population that compare Bring the Low Risk group in the cohorts to the US. General population. As we can see, the Pr increased to 40 to 50%. So this suggests that a large

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* Kresge 502 Cart: proportion of colato cancer instance, can be prevented by simple modification of these lifestyle factors. So again, colorectal cancer is probably one of the cancers that is most strongly associated with these lifestyle factors. So it really highlights the huge potential for prevention of colon cancer.

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* Kresge 502 Cart: So next, I will briefly go over individual risk factors. This is

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* Kresge 502 Cart: the result of smoking was actually the study that had the data almost 30 years ago.

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* Kresge 502 Cart: But it shows that the relationship between years since starting smoking in relation to Colonel cancer risk. And we can see that there is

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* Kresge 502 Cart: nonlinear relationship. The risk of increase did not emerge until the years 35 to 39.

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* Kresge 502 Cart: So this indicates there's a long latency period for the smoking effect on colon cancer. So there's roughly, like a thirty-year induction period for smoking.

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* Kresge 502 Cart: And also.

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* as I mentioned earlier. Colloidal cancer is very heterogeneous. There are different pathways. So if we look at smoking in relation to in relation to different subtypes of colored cancer. We can see that for overall colito cancer. It's pretty modest. The effect size is only 1.2 a for the highest category

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* Kresge 502 Cart: compared to never smokers. But when we classify tumors into different subtests, we can see the red risk is much more substantial for certain molecular subtypes of colored cancer specifically for same high cancer and Msi high cancer. These are the cancers that are considered as serrated cancers that are available through the serenity pathway.

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* Kresge 502 Cart: As I mentioned earlier, the serrated pathway is characterized by hypermethylation and also being deficiency. So we can say there is a very strong relationship indicating that the potential role of smoking in damaging the mismatch repair pathway.

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* Kresge 502 Cart: Maybe the numbers are small. But do you also does it also take that decades long time for Msi cancers that happen, or do they happen? That's great question. Yes, I think substantially, there is data suggesting that

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* Kresge 502 Cart: cerebral cancers tend to divide more rapidly compared to the conventional cancers.

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* Kresge 502 Cart: I will also show some some data later about that. So similar findings have been found for precursor solutions. So here we look at serrated pollens versus conventional Adenoma. As I mentioned earlier, the conventional anoma is considered as the precursor solution for the chromosomal instability pathway, whereas the accelerated pollen is

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* Kresge 502 Cart: precursor for the serrated pathway we can say the association with smoking is much more substantial for serrated pollen compared to convention and normal. So this has clinical implications because the cancers with the serrated features have been identified.

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* Kresge 502 Cart: have

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* Kresge 502 Cart: seem to have a like. The serrated, serrated cancers are more likely to develop after negative colonoscopy.

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* Kresge 502 Cart: This is also related to Laura's question. Like patients with a negative colonoscopy may actually develop a cancer

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* Kresge 502 Cart: very like quickly after the negative exam. So this, like I said, Msi has been characterized

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* Kresge 502 Cart: has been shown to be present in these serrated cancers, and this suggests that for smoking, because smoking is so strongly associated with serrated cancers, it really suggests the potential of prevention for individuals who had a negative colonoscopy to really stop smoking because smoking can

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* Kresge 502 Cart: player can really promote the development of surated cancers, even after an active exam. And unfortunately, we look at our data. And

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* Kresge 502 Cart: for people with

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* Kresge 502 Cart: colonoscopy screening, very few change, like very few participants, really change their lifestyle after the screening, especially for those with an active screening. So there's a long way to go if we look at the risk factor data in our cohorts

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* Kresge 502 Cart: like it doesn't really change much even after people having a positive colonel space screening. And again, this really highlights the potential of epidemiologic data to kind of inform clinical practice.

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* Kresge 502 Cart: not just for our biological understanding, but also for clinical translation and for alcohol. This is a data from the pooling project of 8 cohort studies looking at different dose of alcohol intake in relation to colon cancer risk, we can say again, there seems to be a nonlinear relationship.

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* Kresge 502 Cart: So there is no increase in risk until roughly, like 30 grams per day of alcohol consumption. This is roughly about 2 drinks per day. So for alcohol to influence colorectal cancer. There seems to be a dose like a threshold effect.

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* Kresge 502 Cart: And for Bmi there has been a lot of studies looking at obesity in relation to colorectal cancer. This is a meta analysis summarizing the results, we can see that there is association for both men and women, although for men the association is much stronger than that for women, so the relative risk is about 1 point

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* Kresge 502 Cart: 10 per 5 kg per square meter increase in the mi.

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* Kresge 502 Cart: and this sex difference has been well documented in the literature, not just for colon cancer, but also for other obesity related cancers. And we are still studying what is a mechanism? What is the potential reason for the sex difference? One reason for colon cancer may be related to sex hormones, which I will talk more about that later.

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* Kresge 502 Cart: and in addition to overall, the visual ad central obesity may also have some independent effect. So this is a study that we did. Looking at the Drone Association of Bmi and with conference with cholera cancer risk in women and money. So we classified individuals according to both Bmi

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* Kresge 502 Cart: and also with this conference we can see that for women we didn't see any statistical, significant association. But for men we can see within each Bmi group

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* Kresge 502 Cart: linear relationship for witness conference. A higher waste conference is associated with increased risk of coronal cancer within the same emi category. So this indicates the additional value of facial adiposity for colon cancer.

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* Kresge 502 Cart: and a similar pattern has been shown for other cancers as well.

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* Kresge 502 Cart: So for physical activity. It is also an established protective factor for coloreto cancer. This is a good analysis, and that was originally published. Interestingly, the association is predominantly observed for colon cancer, but also for rectal cancer, for rectal cancer

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* Kresge 502 Cart: not statistically significant, and when the authors looked at moderate versus vigorous agusting, both had an inverse association. But the association is stronger for vigorous, vigorous activity compared to moderate activity. And this is after mutual adjustment

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* Kresge 502 Cart: suggesting that the different effects of different activity tasks.

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* Kresge 502 Cart: and the second rate behavior has also been associated with higher risk of colon cancer. This is the result from the analysis looking at total saving time, TV billing time and also occupational saving time.

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* Kresge 502 Cart: So we can see for all 3 exposures there is a positive association. And interestingly, the association is much stronger for digital colon cancer compared to rectal cancer. And it's pretty weak for proximal colon cancer.

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* Kresge 502 Cart: So digital colon cancer is includes the cancer studies in the like

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* Kresge 502 Cart: after the the splendid flexure descending, cooling, sigmoid and proximal cooling includes the ascending cooling and the transfers, and also the sick. So there has been a lot of etymology data indicating the molecular and risk factor difference across the subset.

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* Kresge 502 Cart: and this subset difference also is also associated with the molecular profiles, so the storage cancers are more likely to develop in approximal coding, and the conventional cancers are more likely in the digital coding. So

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* Kresge 502 Cart: the general like conclusion is that thisal colon cancer is most generally associated with

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* Kresge 502 Cart: lifestyle factors, particularly the metabolic risk factors, including obesity, secondary lifestyle, and the proximal colon cancer has been most strongly associated with smoking and some inflammatory risk factors. So there's a lot of

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* Kresge 502 Cart: like heterogeneity within collateral cancer. That's how the molecular technology can be really helpful.

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* Kresge 502 Cart: So for western data, again, we can say that western data is much more strongly associated with distroin cancer, and then rectal cancer and proxy

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* Kresge 502 Cart: trading week. An Association party week.

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* Kresge 502 Cart: and among Western diet repelling red and processed meat is the strongest risk factor, particularly for processed meat. As we can see from the Meta analysis, the right risk

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* Kresge 502 Cart: is very high for processed meat compared to Rami, I mean for RAM meat there are still some positive associations, although the aftermath is less consistent compared with that for processed meat.

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* Kresge 502 Cart: So to summarize, this is from the review that others wrote few years ago regarding the mechanism so like the unhealthy data lifestyle sent to be in promoting cholera cancer by the insulin and Igf one pathway. So this all health

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* Kresge 502 Cart: lifestyle factors can increase the production of insulin and also the higher level of Igf. I. Both of these hormones can induce cell proliferation and reduce apoptosis that can promote cancer growth.

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* Kresge 502 Cart: So this is the.

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* Kresge 502 Cart: I would say, a pretty well-established pathway. But there is also other pathways that also play a role such as the inflammation and the microbound.

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* Kresge 502 Cart: So is there any questions about the risk factors?

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* Kresge 502 Cart: Okay, so next, I want to briefly talk about the factors that may decrease risk of collateral cancer. Here are there major factors that have been studied, including vitamin d calcium for a fiber aspirin and a hormone replacement therapy, and therefore the 3 factors with a star that indicates the evidence from randomized

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* Kresge 502 Cart: clinical trials. In other words, these 3 factors have been pretty well established to have a protective effect on colored cancer.

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* Kresge 502 Cart: So just briefly going through each of them. For Nvd, the original hypotheses actually comes from the ecological study. So there was the vision that people living in the South America are less likely to develop color compared to people living in the northeast.

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* Kresge 502 Cart: like in the north, particularly northeast. So

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* Kresge 502 Cart: And then that was hypothesis when Med was hypothesized to be a potential factor

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* Kresge 502 Cart: in the mentality. And then, after that, there has been numerous epidemiological studies assessing the binding levels in cohort studies. So this is a recent publication from the International Pooling project that includes 17 cohorts that measure levels among over 5

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* Kresge 502 Cart: cancer cases. We can see that there is a general inverse relationship between binding D levels and cancer risk.

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* Kresge 502 Cart: Here I also included the Institute of Medicine Guidance for bone health. Regarding Bambidi status for people with deficient and insufficient they tend to have a higher risk of cancer compared to individuals with sufficient or even higher

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* Kresge 502 Cart: 2,

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* Kresge 502 Cart: and a similar inverse association has been observed for calcium. For calcium. There seems to be. There seems to be a nonlinear relationship, as we can see here the benefit of levels of at about 1,500 microgram per day consumption.

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* Kresge 502 Cart: So after that the risk did not continue to decrease.

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* Kresge 502 Cart: and for foli there is a very interesting latency effect. So if we look at the Folate intake of prayer to colorectal cancer diagnosis there is no association. The lamp is pretty flat, but when we look at when we look at the intake

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* Kresge 502 Cart: 12 to 16 years prior to diagnosis with a pretty substantial inverse association between higher folate levels for higher foliage intake and lower cholesterol cancer instance. So this indicates that it is folate intake that is.

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* Kresge 502 Cart: decades before that really influenced cancer risk. In other words, if we want to prevent colorectal cancer by fully supplementation or other method. The supplementation has to happen early.

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* Kresge 502 Cart: much early in life in order to have to say benefit like Wow. years later.

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* Kresge 502 Cart: and the fiber is another beneficial mutual nutritional factor that has been linked to colorectal cancer. Instance, as we can see from this analysis, there's about 10% reduction for each 10 gram per day intake of divergent fiber. And we can see that the association is pretty consistent across studies, especially for studies with larger sample size.

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* Kresge 502 Cart: And there's also a pretty linear relationship in the dietary, fiber intake and cancer. Instance.

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* Kresge 502 Cart: if we put intake particles in this graph, like the average intake in this country, is about 16 grams per day, which over here the recommended intake is 28 to 34 grams per day, which is over there, and as we can see if we increase the fiber intake for everyone to the recommended level, there can be a substantial public health impact on colonial cancer prevention.

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* Kresge 502 Cart: So this is just to show you the potential of primary prevention for colon cancer, even for a single battery factor.

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* Kresge 502 Cart: If you I didn't touch on the mechanisms. But if you want to learn more about how this nutritional factor may influence colon cancer risk. You can refer to the review that we wrote a few years ago, summarizing all the different pathways.

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* Kresge 502 Cart: And also I want to mention that for these nutritional factors the observational data have been pretty compelling also quite consistent. But for the clinical trials. As you may have learned from the media, from the literature, the evidence is less clear, so most the nutritional innovation studies did not actually say, a benefit

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* Kresge 502 Cart: for cancer prevention, including for a calcium and even fat, maybe D. So here are some of the reasons that

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* Kresge 502 Cart: we should be very careful about like when we interpret the findings for the clinical trials. So one reason, maybe the appropriate time window of intervention. So most of the individual studies for Colon Cancer Prevention have enrolled patients with a history of polyps. So, as I mentioned earlier, Pollux is a precursoration of colon cancer. Individuals with polyps

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* Kresge 502 Cart: have already had the carcinogenic process started. So we may have missed the critical time of cancer initiation. This is particularly true for Folate, because it has been shown that if we give patients with an enormous foliage supplementation supplement.

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* Kresge 502 Cart: they actually have a higher risk of developing colonial cancer. So it's possible that Poly may actually promote the cancer development among individuals with early precursor issues. In other words, among individuals whoseogenic process has already started giving them folly can be harmful rather than beneficial.

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* Kresge 502 Cart: and another reason is inappropriate dose. So for one, maybe the dose that was used in the Who, which is one of the largest intro trial in nutritional studies women's health initiative. So they use the 400 Iu per day. And

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* Kresge 502 Cart: this is actually very small, like, if we look at the plasma vitamin D levels. The 400 IU only increase only lead to a very modest increase in plasma levels. And that's why the more recent vital study, the vitamin d. And facial oil trial used as a 2,000 iu.

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* Much higher dose to test whether there's any benefit. And another reason may be because participants

45:05

* Kresge 502 Cart: already sufficient in their intake for these nutritional factors, for example, for calcium in the who in the Women's Health Initiative, their baseline intake is already over. The 1,000 micrograms per day dose that I showed earlier after 1,000 micrograms per day. There's actually no further reduction in credit

45:14

* Kresge 502 Cart: concern in space. In other words, if all individuals start here, if we give them calcium supplementation, we won't be able to see any benefit.

45:39

* Kresge 502 Cart: And finally, like most of the clinical trials, have very limited duration less than 5 years, so they show the duration may not be sufficient to observe benefit, especially for factors that have a long latency period, such as folding. So this is just some considerations

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* Kresge 502 Cart: to to to take into account when we interpret the observational findings versus the innovation results. So as etymologists just don't. We shouldn't just take the results at a Facebook value. And really to need to think about the alternative interpretation and to

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* interpreted the totality of the literature

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* Kresge 502 Cart: there any questions or comments about it regarding this.

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* Kresge 502 Cart: this is very relevant to the the the talk that Ed gave on diet and cancer. So I'm wondering also kind of given the conversations about the different studies design, so do you have any other thoughts, or that where you might see differences between the Rcts and epidemiologic studies.

46:49

* Anything else that you can think most.

47:07

* Kresge 502 Cart: Yeah, I have. Probably I have already mentioned this, like for medication. Clinical trial is probably the good standard. But for nutrition there's a lot of problems with the clinical trial, and we really should be very cautious. Yes.

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* Kresge 502 Cart: is that adjusted for anything. I don't think so. It's just that it's age adjusted. But other than that, it didn't adjust for anything

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* Kresge 502 Cart: like even more different diet.

48:02

* Kresge 502 Cart: not to generalize regions. That's good point. I'm I'm not sure. I mean, this is a historical data, right? From 1,900 seventys to 1,990. And since then, like I mentioned earlier, a lot of things have changed. I actually, I can't remember. I need to check if the pattern still remains nowadays.

48:11

* Kresge 502 Cart: Attitude right?

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* Kresge 502 Cart: It's a bit weaker now, but it could be related if it is actually the sun

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* Kresge 502 Cart: that the patterns of sun exposure got very different. 19 sixties.

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* Kresge 502 Cart: Yeah, just I feel like,

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* Kresge 502 Cart: At that time. Probably there seemed like more. I mean, the epidemiologic pattern has changed very dramatically over the past few decades. But still I feel like the ecological study can be really beneficial to

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* Kresge 502 Cart: get some initial clue like, especially for early onset cancers. Since we really don't know the reason this kind of ecologic study can be beneficial or can be helpful for hypothesis generation.

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* Kresge 502 Cart: Besides the diary factors, some medications have also been linked to lower risk of colon cancer. Aspirin is the most established medication. As we can see, this is from a pool analysis of fat, randomized, controlled trials. We can see there is a very strong diverse association

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* Kresge 502 Cart: between aspirin use and a lower risk of colon cancer, and the Association is much stronger for proximal colon cancer. Again, this goes back to my earlier comment regarding the subset difference, the proximal colon cancer is more related to the serrated pathway and more related to the inflammation, inflammatory mechanisms. So this

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* Kresge 502 Cart: it fits in pretty well, like aspirin, may reduce the risk of proximal coral, and also, when we look at the treatment duration we can see here.

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* Kresge 502 Cart: like only like the inverse association, was only from for the trials with at least 10 years of treatment. So again, it highlights the latency effect for aspirin as well. It takes about 10 years to really see a benefit. Similarly, as we can see from this study, the women's health study, which is a large, randomized, controlled trial with 100 microgram

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* Kresge 502 Cart: per day. This is considered a low dose, and also alternate alternate day as per use. We can see that it takes about 10 years to really see a separation between the intervention group and the control group.

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* Kresge 502 Cart: So the solid line is Aspirin Group, and the dash line is a control group, and we can say that 2 lines did not separate until 10 years

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* Kresge 502 Cart: after the invention. Again.

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* Kresge 502 Cart: it highlights the the importance of having long duration in order to see a benefit for this

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* Kresge 502 Cart: protected factory, and you may have learned from the the press. There's also a concern about like aspirin use among other individuals. So this is from the recent aspirate trial. This study enrolled patients who are like

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* Kresge 502 Cart: at least 70 years old, so they wanted to say whether they should also take aspirin because aspirin can be beneficial for colon cancer and also for cardiovascular disease prevention, and for older individuals is very poor. So they conducted this large randomized control to test the benefit of aspirin use

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* Kresge 502 Cart: among all the individuals, and we can see here. Interestingly, the Aspirin group actually had a higher risk of cancer death compared to the placebo group.

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* Kresge 502 Cart: and and as a positive association was observed for many cancers, including collaborative cancer. As we can see here, the relative risk is pretty high is 1.7,

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* Kresge 502 Cart: and because of this result, in 2,022. The US. Preventive Services task force no longer recommends aspirin use for colato cancer prevention like before 2,022. The recommendation was to use aspirin for prevention of colon cancer among adults.

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* Kresge 502 Cart: even average risk adults. But because of this funding the Uspsf. They stopped the recommendation for Colon cancer prevention, although we know that the evidence comes from old individual and does not apply to the young adults.

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* Kresge 502 Cart: But still the recommendation changed dramatically. And also.

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* Kresge 502 Cart: Another reason is because of the bleeding risk. Aspirin is associated with higher risk of bleeding, particularly gi bleeding. So the the I guess the task force was very cautious about this, and no longer aspirin.

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* Kresge 502 Cart: and completely for all individuals, regardless of being at higher risk for colon cancer. For Cbd there is still recommendation for the high risk.

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* and I mean we still don't know why, like what is causing the increase among older individuals.

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* Kresge 502 Cart: Whether this is related to the biology, or how aspirin works in older individuals versus young individuals. It is related to the characteristic of the participants in this clinical trial, and there will be longer follow up, and the trial is still under active follow up. So there will be more data

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* Kresge 502 Cart: after longer. Follow up time, because the the the

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* Kresge 502 Cart: the the unit. And the publication was people like roughly after 6 years of information.

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* Kresge 502 Cart: So another medication that has been linked to lower risk of colon cancer is the hormone replacement therapy, as we can see from the Women's Health Initiative, a large clinical trial. Comparing the effect of estrogen plus progester versus placebo. We can see there is much lower

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* Kresge 502 Cart: colonial cancer instance in the treatment group compared to the controls.

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* Kresge 502 Cart: And there has been

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* Kresge 502 Cart: really well documented biological pathways regarding how estrogen may actually protect against colorectal cancer through the estrogen receptor which is widely expressed in the colorectal mucosa. And this may actually explain some of the sex difference in cancer risk factors, women, especially the post menopausal women.

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* Kresge 502 Cart: Their major source of astrology is from the adiposity from the adipose tissue, so that may explain why, obesity is

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* Kresge 502 Cart: much weekly, very weekly, associated with colon cancer compared to that in mind, so the estrogen may offset some of the adverse effects of obesity.

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* Kresge 502 Cart: and then another emerging risk factor is got macrobound. You probably have learned before that macrobound is considered as another organ of our human body, and it plays an essential role in both the metabolism, immunity, and also in adaptory

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* Kresge 502 Cart: absorption. So that's why we propose that this kind of triangle model and a way

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* Kresge 502 Cart: hypothesized that it is the interplay between diet microbes and the host factors that together determines cancer risk. This is particularly true for colorectal cancer. Given that the largest number of bacteria in our human body lives in the gut.

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* Kresge 502 Cart: and there have been some microbes linked to a higher risk of colon cancer and some linked to lower risk of coronal cancer. And here, at least, the bacteria that have established to play a role in colon cancer development.

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* Kresge 502 Cart: And right now the evidence from under microbound is largely from retrospective studies like a piss control study. We still don't know whether microbound changes are a cause or a consequence of colon cancer development.

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* Kresge 502 Cart: That's why we are establishing a prospective cohort in the nurses have studied 2 trying to understand the role of the baseline, how it may predict subsequent risk of colorectal cancer and other diseases. So we are collecting macrobound samples from women in the nurses have studied 2 cohort.

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* Kresge 502 Cart: and because these swimming are still under active follow up. We will have instant cancer cases after still an oral sample traction to prospectively study the role of microbes in cancer development.

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* Kresge 502 Cart: So I can imagine there will be more fundings coming up in the last few years from the school.

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* Kresge 502 Cart: So that's all for primary prevention. If there are any questions about the risk factor or protective factors.

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* Kresge 502 Cart: Okay? If not, we can move on to the secondary prevention, which is about a screening basically to detect the cancer early for

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* Kresge 502 Cart: detect and also remove the detector cancer early and then remove the precursor lesions, so called parlors. So this is data from the observational studies looking at colonoscopy screening in relation to colorectal cancer, incidence, and mortality, we can see that there is a very strong inverse association for both incidence and mortality.

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* Kresge 502 Cart: Sorry. These are based on epidemiological data clinical trials. Yes, yeah. And this is from clinical trials. This is from the Nordic trial, which was, I think, published in 2,022. It's a very interesting study design. They use the pragmatic trial, basically the grandma's individual first.

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* Kresge 502 Cart: and then they only consent. Individuals who are randomized into the intervention group.

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* Kresge 502 Cart: and over 84,000 healthy adults were enrolled into either colonoscopy or usual care, and the participant rate a participation rate in the colonoscopy group is pretty low, as we can see only 42. In other words, among those who are randomized to the colonoscopy group, only 42% of those really received the colonoscopy.

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* Kresge 502 Cart: And but for the analysis, because it's a randomized trial, they still use the intended to treat design. So the results here is still based on the intended to treat analysis as we can see here, for instance, the relative risk is about 0 point 8 2, and for mortality is 0 point 9. So it's much, much weaker than the observational data, like 130.

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* Kresge 502 Cart: So I guess the reasons why is that the case.

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* Kresge 502 Cart: I want you, yeah, we can maybe have some discussion. That sounds good. So here, all the essential data about the trial and about the data about the results.

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* Kresge 502 Cart: I think I had forgotten about the the fact that the the on the incident.

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* Kresge 502 Cart: so for the sake of time we publish started a discussion any thoughts why, the results are much weaker from this trial compared to the observation data. As an epidemiologist, how to interpret the observation of universal funding is probably one of the most critical questions

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* Kresge 502 Cart: here I list a few issues to consider.

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* Let's start with pragmatic design.

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* Kresge 502 Cart: Do you guys see the difference between this study design versus the traditional trial design, because in the traditional clinical trial we normally would do the consent. First, only individuals who give the consent will be randomized to the treatment of plausible group. But in this trial they actually randomize individuals first, and then collect the consent only from the treatment group.

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* Kresge 502 Cart: Any thoughts like, why, the, in fact, is so weak.

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* Kresge 502 Cart: Yes.

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* parts of the observation on one. Here we are doing intention to treat so more than half of the people that were supposed to publicly.

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* Kresge 502 Cart: they call most of the dealing actually receives. So we are underestimated. Yeah, yeah, that's definitely one object

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* Kresge 502 Cart: potential reasons, because the low participation rate in the innovation group. Can you guys see some athletes to support from the 2 figures

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* Kresge 502 Cart: like, let me ask first for the business speaker. Are you surprised? The better? Crossing

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* Kresge 502 Cart: between the 2 groups, like the blue is the control group, and the red is an intervention group.

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* Kresge 502 Cart: So they cross over

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* Kresge 502 Cart: at about 6 years after intervention, I mean, after the start of their trial.

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* Kresge 502 Cart: is this expected or unexpected?

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* Hi.

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* Kresge 502 Cart: like regularly the usual treatment? So if they already have the usual treatment. Then it comes

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* Kresge 502 Cart: detected. There is.

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* Kresge 502 Cart: And, for example, in the earlier ages, like in their year. Sorry

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* Kresge 502 Cart: because we are.

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* Kresge 502 Cart: It's mainly like a detection. But we are detecting the prevalent cancers from the population. That's why the instance is actually higher in the innovation group compared to the control group. But why? The instance gets lower in the Innovation group?

1:07:00

* Yes.

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* Kresge 502 Cart: exactly. And also you can remove the polyps, which is a precursor addition. So I realize not all of you. So the colonoscopy does not only detect cancer or polyps, it can actually remove the lesions, and it can be both

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* Kresge 502 Cart: considered as both preventive and also to some extent therapeutic. It can actually remove the precursation. That's why the incidence gets lower over time. So this is pretty commonly observed for conduct, space for clinical trials. But are you surprised? Let me ask it this way for mortality. Do you expect a similar crossover, or

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* Kresge 502 Cart: you wouldn't expect

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* to.

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* Kresge 502 Cart: Yes, because if you're in the area, then

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* the risk of life progressing to the cancer itself prices because

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* Kresge 502 Cart: you gave me call it?

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* Kresge 502 Cart: Oh, yeah.

1:08:56

* Kresge 502 Cart: yes.

1:09:09

* Kresge 502 Cart: I mean from the death certificate, you will still know, like I mean, it's likely like a son may not be diagnosed even at a death, but that's

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* Kresge 502 Cart: unlikely, I think, in the in the.

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* Kresge 502 Cart: in general, like

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* Kresge 502 Cart: people who die from colon cancer like, they also probably have received a diagnosis before.

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* Kresge 502 Cart: So the detection bias is actually normally is only observed, for instance, but not for mentality. And this is. I guess, for me this is unexpected for mentality. We wouldn't expect such crossover for mentality, and the fact that the Innovation group had a higher mortality, like, as you can see roughly like 4 to 7 years, suggest that there's something with the innovation group, right?

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* Kresge 502 Cart: So because of the low. Again, because of the low participation rate, it is possible that individuals who are at high risk, either based on beneficially based on their perceived risk, they may be more likely to receive the colonoscopy. They may be more likely to participate, and that may lead to their higher mortality compared to their control group.

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* Kresge 502 Cart: And that's why I think it will be very interesting to compare the risk factor information in the

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* Kresge 502 Cart: in 2 different groups to say what exactly

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* Kresge 502 Cart: what a group of patients of individuals are really participating in the trial, to figure out what's going on with the contribution of low participation grade.

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* Kresge 502 Cart: So let me ask a group question. So for the incidents, that part, is it possible that

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* Kresge 502 Cart: a participant rate is higher. In the early years since randomization

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* Kresge 502 Cart: probably invited me. The partisan

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* Kresge 502 Cart: doesn't participate or take less of scope.

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* Kresge 502 Cart: After many years of the migration, maybe like 5 to 10 years after resignation. So their autism rate gets decreased too. So you are seeing this is because the innovation group gets north in time

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* Kresge 502 Cart: after a recommendation.

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* Kresge 502 Cart: 10 rains like would change during years. Yeah, I think the 42% is average. There may be some variation over time.

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* Kresge 502 Cart: like maybe, like in the early years there's a higher participation. And then it went down. Yeah.

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* Kresge 502 Cart: but I wouldn't expect that's a good point, because the baseline is a recommendation. So there is left truncation people who have to be randomized, and for the innovation group it may take some time for them to receive the colonoscopy after randomization. So there is the left truncation issue.

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* Kresge 502 Cart: And I'm also curious about the observations. Oh, so for observational study, it is just comparing individuals who receive the colonoscopy versus who did not. So it's based on that observational data. It's not like all.

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* Kresge 502 Cart: So we won't discuss that because you can consider the observational study as comparing those who receive the innovation compared to the rest of the individuals, whereas in this clinical trial they are comparing the individuals who were randomized to intervention versus those who were randomized to to control.

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* Kresge 502 Cart: So that's why I guess.

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* Kresge 502 Cart: what is the trial measuring right in this study? It's measuring different things compared to the observational study.

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* Kresge 502 Cart: Thank you. Yeah, so yeah, normally for randomized clinical trial, we are interested in efficacy. In other words, we are interested in the true effect

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* Kresge 502 Cart: in a controlled sighting. But in this study, because of the pragmatic design, what they are measuring is actually that effectiveness rather than efficacy

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* Kresge 502 Cart: that may also contributed to the much weaker effect.

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* Kresge 502 Cart: Oh, you need time. Now, what do you mean by time? Like, Oh, I see. Okay, yeah. And like, it definitely can influence like. For colonoscopy. Normally, it's recommended every 10 years like after negative chronoscopy, right? Like it's possible some individuals make repeated colonoscopies. But like II don't think that's accounted for in the analysis. Yeah.

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* Kresge 502 Cart: then, in the observational data, they just considered any chrominosphere some individuals may get one. Some may get 2 or more.

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* Kresge 502 Cart: Yes.

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* Kresge 502 Cart: death. Yes, I mean right to answer specific

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* Kresge 502 Cart: I think it is. I think it is the Colorado concern, specific to death. But I can double check. Yeah, like a communication. Right? Yeah, that's good point.

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* Kresge 502 Cart: I think it is colon cancer specific there. So this is a current screening guidelines. So because of the increase in early onset cancer screening, the starting age has been lowered to 45 from 50. It used to be 50, and now it's 45,

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* Kresge 502 Cart: and continued until 75. And there are different options besides colonoscopy. But colonoscopy is still the most popular method in this country.

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* Kresge 502 Cart: and there's a lot of issues with cholera to cancer screening. First one is still the sub optimal uptake and disparity. As we can see, the uptake rate varies across the States.

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* Kresge 502 Cart: and probably, I think Massachusetts has one of the highest rates across the country, and in general the uptake has been increasing, but for Hispanics, as we can see it still lags behind other racial groups.

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* Kresge 502 Cart: And there is also the concern about interval. Cancer, like individuals who had a negative colonoscopy, may still get colorectal cancer before their next recommended colonoscopy.

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* Kresge 502 Cart: and we are still figuring out what is causing the info cancer, and, as I mentioned earlier, the serrated cancers are more likely to occur in the interval after negative Columbus.

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* Kresge 502 Cart: and there is still uncertainty regarding when to start and when to stop screening, and the starting age was lowered mainly because of the rising incidence of early onset cancer. But there is a lot of concern about the overuse of screening among healthy, low risk young individuals.

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* Kresge 502 Cart: whereas the the for the only individuals who are at high risk, they may not get the colonoscopy in a family manner. There is also the

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* Kresge 502 Cart: concerned about the aging right as the population is aging, whether we should also extend the stop age of colonoscopy to an older age. Right now it's 75,

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* Kresge 502 Cart: and there is a potential for personalized or precision prevention, because colonoscopy is very expensive and it is very invasive. It carries some very severe complications, so it makes sense from the population perspective to tailor the chromosome to individuals who need them most. So this is a study that we did.

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* Kresge 502 Cart: trying to look at the risk of profiles. According to risk factors. As we can see, we considered the major risk factors for colon cancer. And we plot the age-specific colon cancer instance, we can see that if we draw some line

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* Kresge 502 Cart: to indicate when to start a conduct based screening for the high risk individuals, they may start as early as 44 years old for older individuals and for the low risk individuals. They may not admit it until age 56, because their risk did not gather to the same level until very later in time. So that indicates the potential for personalized screening.

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* Kresge 502 Cart: And finally, I just want to briefly talk about terra prevention. Turf prevention is about improving survivorship among patients with established cancer. And we have been studying the role of lifestyle in improving colonial cancer survivorship. As I mentioned earlier, there is an increasing number of cancer survivors

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* Kresge 502 Cart: who are really eager to adopt lifestyle modification in order to facilitate their prognosis and treatment, but there are a lot of challenges with observational data, reverse causality conforming, and also the heterogeneity by stage and treatment, and also some exposure may become part of the clinical cause of the disease, such as weight loss. So it's really

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* Kresge 502 Cart: difficult to study how these risk factors may influence prognosis after cancer diagnosis, and these people just summarize the factories that have been linked to colon cancer survival after diagnosis.

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* Kresge 502 Cart: And right now, what I'm most interested in is actually coffee, because it has been showing to be beneficial across different observation studies, and the findings have been very consistent. And right now we are doing a randomized, controlled trial to test the benefit of coffee among cold patients. So, again, trying to integrate observational studies

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* Kresge 502 Cart: with clinical trials, to better understand the risk factors

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* Kresge 502 Cart: and to summarize colon cancer is highly preventable by screening and also by lifestyle modifications, and while screening is warranted that lifestyle factors should still be the predominant factors to consider for prevention and studies on the interplay between data and a microbiome will prove by important mechanistic and translation inside

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* Kresge 502 Cart: in the future, and in more studies, preferably clinical trials are needed to understand the role of data lifestyle in terms of survivorship.

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* Kresge 502 Cart: because, compared to instance, the survivorship, the innovation doesn't take that long to see an outcome among patients with colonial cancer. So we need more clinical trials to better understand the role of these risk factors

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* Kresge 502 Cart: and to summarize. This is all the factors that we have considered in this lecture regarding their role in the natural natural history of coloreal cancer. Some of the risk factors really play a role in the early stage of cancer development. That's why there's a long latency period for other factors. They are more likely to play a role

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* Kresge 502 Cart: in the intermediate or even in the late phase of cancer development.

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* Kresge 502 Cart: So this is what I do. And I'm happy to answer any questions you may have feel free to email me if you are interested in studying colon cancer as I showed you in this lecture, there are still a lot of unknowns to be studied for Colonel.

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* Kresge 502 Cart: Thank you.

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* Any remaining thoughts or questions.

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* Kresge 502 Cart: Yes.

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* really. Come up on that massive. It's like, completely, I don't know.

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* Kresge 502 Cart: Oh, I see. Okay. Oh, okay.

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* Kresge 502 Cart: yeah, yeah, thank you for checking. Yeah, I guess not. Surprising is the infiltration of the unhealthy lifestyle across the country.

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* Kresge 502 Cart: Thank you.

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* Kresge 502 Cart: Great. Thank you. So much excellent.

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* Kresge 502 Cart: What do you want us to do here?