Cancer epitia. Today's question is which of the following cancers has the lowest estimate of heritability. No melanoma's in the clear lead right now. Some of them voted for testicular cancer. Testicular cancer is a fascinating cancer. I don't think, unfortunately, anyone signed up for it for the project. Melanoma and prostate cancer are tied for the 2 cancers that have the highest estimate variability. Melanoma is interesting. It actually has a really strong family history. A person has a brother or a father who had cicular cancer. Their own risk of Cisco cancer is substantially elevated. Colon cancer ends up being the cancer with the lowest estimate of heritability. About half of that family history is actually due to some shared environmental factors. So great, excellent! Introduce. Don't say too much. I was lucky to get me young as my student he was a great, great student. Dimitri: 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. Dimitri: Yeah, it was one of the most impressive lectures that I have ever taken. Colorectal cancer ranks. the third in both men and women, and also for both incidents and mentality. It comes for about 8 to 9% of deaths among all cancers. So it's definitely still a major cancer in this country. It's actually good, because I was deciding to cut. although last year as well. In the past few decades, as we can see, luckily both incidence and mortality have been declining. 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 the previous year. 53% of the reduction is likely due to screening. Improvement also accounts for about 35% of decline. This is mainly driven by the reduction in smoking and also other unhealthy lifestyle. Treatment consumes the largest of the economic burden for colon cancer. But compared to the risk factor and the screening, it actually contributes the least. For colon cancer among young individuals below age 50, there is a growing increase. There is a huge, a lot of discussion about what is driving this increase. And interestingly, it's not just like America. It's across the globe, even for some middle or low income countries. 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. The Western States tend to have lower rates in general as a southern stage, have much higher rates. So it's interesting for Colorado, I remember from the obesity IP like it has the lowest obesity. Across all regions there has been an increase after the 1,950 birth cohort. and here the increase is actually most dramatic for East Asia. There has been some projection that over time as the new birth cohort ages. We will also see an increasing instance of Colorado cancer even among older individuals. 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. There are the like possible reasons that have been proposed in the literature, such as obesity, Western diet, and lifestyle. This is particularly relevant to early onset cholera, because for younger individuals their exposure history is much shorter. The critical period, maybe. 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. The totality of the environment that really shapes the microbiome. I mainly focus on the gut microbound. That for microbound, our understanding is still very premature. It's still a green area. So next, I want to briefly talk about the molecular features and the natural history of colorectal cancer. The 2 pathways are very different molecular. One is the chromosome or instability Pathway. 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. So cancers developing through this pathway is characterized by microsatellite instability and also hypermethylation. The microsatellite instability pathway is also called a serrated pathway, because it's characterized by the precursor illusion, serrated columns. And these 2 different pathways also contribute to histologically different praker solutions. So again, it really highlights the heterogeneity of Colorado cancer. not just molecular, but also risk of actor wise. Smoking alcohol obesity, sedatory lifestyle. Red are processed meats and Western diet in general. Low Risk group is defined by a combination of all these different, like 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. This suggests that a large proportion of colato cancer instance, can be prevented by simple modification of these lifestyle factors. So it really highlights the huge potential for prevention of colon cancer. The risk of increase did not emerge until the years 35 to 39. So there's roughly, like a thirty-year induction period for smoking. The effect size is only 1.2 a for the highest category compared to never smokers. But when we classify tumors into different subtests, we can see the red risk is much more substantial. There is a very strong relationship indicating that the potential role of smoking in damaging the mismatch repair pathway. There is data suggesting that cerebral cancers tend to divide more rapidly compared to the conventional cancers. So similar findings have been found for precursor solutions. So here we look at serrated pollens versus conventional Adenoma. Serrated, serrated cancers are more likely to develop after negative colonoscopy. This is also related to Laura's question. Like patients with a negative Colonoscopy may actually develop a cancer very like quickly after the negative exam. So this has clinical implications because the cancers with the serrated features have been identified. Msi has been characterized has been shown to be present in these serrated cancers. For people with colonoscopy screening, very few change, like very few participants, really change their lifestyle after the screening. So there's a long way to go if we look at the risk factor data. There is no increase in risk until roughly, like 30 grams per day of alcohol consumption. This is roughly about 2 drinks per day. There seems to be a dose like a threshold effect. For men the association is much stronger than that for women. The relative risk is about 1 point 10 per 5 kg per square meter increase in the mi. A higher waste conference is associated with increased risk of coronal cancer within the same emi category. This indicates the additional value of facial adiposity for colon cancer. For women we didn't see any statistical, significant association. But for men we can see within each Bmi group linear relationship for witness conference. Physical activity is also an established protective factor for coloreto cancer. The association is predominantly observed for colon cancer, but also for rectal cancer. A similar pattern has been shown for other cancers as well. And the second rate behavior has also been associated with higher risk of colon cancer. Digital colon cancer is includes the cancer studies in the like after the the splendid flexure descending, cooling, sigmoid and proximal cooling. And interestingly, the association is much stronger for digital colon cancer compared to rectal cancer. And it's pretty weak for proximal colon cancer. So the general like conclusion is that thisal Colon cancer is most generally associated with lifestyle factors. Western diet repelling red and processed meat is the strongest risk factor, particularly for processed meat. So there's a lot of like heterogeneity within collateral cancer. So this all health lifestyle factors can increase the production of insulin and also the higher level of Igf. 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 clinical trials. Both of these hormones can induce cell proliferation and reduce apoptosis that can promote cancer growth. There is also other pathways that also play a role such as the inflammation and the microbound. There is a general inverse relationship between binding D levels and cancer risk. A similar inverse association has been observed for calcium. 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 2. 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. So after that the risk did not continue to decrease. and for foli there is a very interesting latency effect. If we want to prevent colorectal cancer by fully supplementation or other method. The supplementation has to happen early. much early in life in order to have to say benefit like Wow. years later. There's about 10% reduction for each 10 gram per day intake of divergent fiber. The association is pretty consistent across studies, especially for studies with larger sample size. If we increase the fiber intake for everyone to the recommended level, there can be a substantial public health impact on colonial cancer prevention. Most of the individual studies for Colon Cancer Prevention have enrolled patients with a history of polyps. Pollux is a precursoration of colon cancer. Individuals with polyps have already had the carcinogenic process started. So we may have missed the critical time of cancer initiation. Poly may actually promote the cancer development among individuals with early precursor issues. This is particularly true for Folate, because it has been shown that if we give patients with an enormous foliage supplementation supplement they actually have a higher risk of developing colonial cancer. and another reason is inappropriate dose. There's actually no further reduction in credit concern in space. And another reason may be because participants already sufficient in their intake for these nutritional factors. 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. 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. And really to need to think about the alternative interpretation and to interpreted the totality of the literature there any questions or comments about it regarding this. 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 get some initial clue like, especially for early onset cancers. Besides the diary factors, some medications have also been linked to lower risk of colon cancer. There is a very strong diverse association between aspirin use and a lower risk of colon cancer, and the Association is much stronger for proximal colon cancer. So this it fits in pretty well, like aspirin, may reduce the risk of proximal coral. Like only like the inverse association, was only from for the trials with at least 10 years of treatment. It takes about 10 years to really see a separation between the intervention group and the control group. aspirin can be beneficial for colon cancer and also for cardiovascular disease prevention, and for older individuals is very poor. It highlights the the importance of having long duration in order to see a benefit for this protected factory. The US. Preventive Services task force no longer recommends aspirin use for colato cancer prevention. The recommendation was to use aspirin for prevention of colon cancer among adults even average risk adults. 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. For Cbd there is still recommendation for the high risk. and I mean we still don't know why, like what is causing the increase among older 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. Estrogen may actually protect against colorectal cancer through the estrogen receptor. This may actually explain some of the sex difference in cancer risk factors, women, especially the post menopausal women. macrobound is considered as another organ of our human body. It plays an essential role in both the metabolism, immunity, and also in adaptory absorption. The largest number of bacteria in our human body lives in the gut. 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. But right now the evidence from under microbound is largely from retrospective studies. There is a very strong inverse association for both incidence and mortality. So we are collecting macrobound samples from women in the nurses have studied 2 cohort. and because these swimming are still under active follow up. We will have instant cancer cases after still an oral sample traction to study the role of microbes in cancer development. The Nordic trial, which was, I think, published in 2,022, is a very interesting study design. They use the pragmatic trial, basically the grandma's individual first. and then they only consent. And the participant rate a participation rate in the colonoscopy group is pretty low, as we can see only 42. How to interpret the observation of universal funding is probably one of the most critical questions. Let's start with pragmatic design. Do you guys see the difference between this study design versus the traditional trial design? In the traditional clinical trial we normally would do the consent. But in this trial they actually randomize individuals first, and then collect the consent only from the treatment group. More than half of the people that were supposed to publicly. they call most of the dealing actually receives. So we are underestimated. Low participation rate in the innovation group. Can you guys see some athletes to support from the 2 figures like, let me ask first for the business speaker. The colonoscopy does not only detect cancer or polyps, it can actually remove the lesions, and it can be both considered as both preventive and also to some extent therapeutic. That's why the instance is actually higher in the innovation group compared to the control group. 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? So 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. In the early years since randomization probably invited me. The partisan doesn't participate or take less of scope. 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 after a recommendation. 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 that's why I guess. what is the trial measuring right in this study? It's measuring different things compared to the observational study. The study found that effectiveness rather than efficacy may also contributed to the much weaker effect. For colonoscopy. Normally, it's recommended every 10 years like after negative chronoscopy, right? But like II don't think that's accounted for in the analysis. Then, in the observational data, they just considered any chrominosphere some individuals may get one. Colonoscopy is still the most popular method in this country. Massachusetts has one of the highest rates across the country. For Hispanics, as we can see it still lags behind other racial groups. 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 colonoscopies. Serrated cancers are more likely to occur in the interval after negative Columbus. There is still uncertainty regarding when to start and when to stop screening. 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. It makes sense from the population perspective to tailor the chromosome to individuals who need them most. 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. And finally, I just want to briefly talk about terra prevention. There is an increasing number of cancer survivors who are eager to adopt lifestyle modification in order to facilitate their prognosis and treatment. Right now, what I'm most interested in is actually coffee, because it has been showing to be beneficial across different observation studies. And right now we are doing a randomized, controlled trial to test the benefit of coffee among cold patients. colon cancer is highly preventable by screening and also by lifestyle modifications. While screening is warranted, lifestyle factors should still be the predominant factors to consider for prevention. Studies on the interplay between data and a microbiome will prove by important mechanistic and translation inside in the future. Some of the risk factors really play a role in the early stage of cancer development. Surprising is the infiltration of the unhealthy lifestyle across the country. There are still a lot of unknowns to be studied for Colonel. If you are interested in studying colon cancer as I showed you in this lecture, feel free to email me.