Laura Lai Moochie: I do mostly cancer epidemiology. With a nutrition focus some frosty but more of a color rectal and like gas for intestinal cancers, although it won't be giving the prostate cancer lecture this year. We actually have 2 amazing teaching fellows here. There's 2 ways to access. The first is you can go open up a web browser and type in POLL.com backslash. The other way you can do it is if you want. If you want to use your cell phone, you can text the number 37607. In the United States, about 40% of cancer diagnoses are thought to be preventable. If you could eliminate all the cancer risk factors, could you actually pre prevent? So is it 7, 2540, or 90? You can enter what you think is the right answer. The course will focus on what are some of the major categories of of what we think are causal factors in the ideology of cancer. We'll also talk about cancers for which we actually don't know as much about in terms of the epidemiology. The course will focus on the descriptive epidemiology of cancer. We'll spend some time, both in class in each of the lectures, as well as one of your assignments, is going to be focused more on that. The focus is really learning to understand the literature from a big picture perspective. We interpret studies individually, but also in the context of other like studies like. ke, you know, like statistical methods. Some lectures will be mostly focused on the disease like specifically breast prostate colon liver and pancreatic cancers. And then in in their class assignments, we'll talk about other cancers that that won't have the big lectures. The classes include presentations by the course instructors. We'll have some interactive learning during the classes which we'll get into later. You have assigned course reading readings. II think it would enhance the lecture. We know that not everybody does. Next week we'll del start delving into the specific topic. So I'll do mostly next week the diet, cancer, obesity, physical activity. So, and then the in class presentations are, February 20 and the twenty-second. And we'll get into that. We have, a few different assignments, and and we tried to make them as sort of things that you could take into the real world with you. One of one of these assignments, which I think we've gotten great feedback on is doing sort of a mock journal critique. So it's learning how being a You'll work in small groups and we'll find out later how how those are. You'll kind of self select and so it'll be focusing on a descriptive epidemiology of a specific cancer. You're so welcome each to discuss the article come up with. There are the cancers for this year, so it's blad, so you only so you'll be in one of these cancers, will be a 1 one of the groups. So bladder and the metro ovarian. sophocus, kidney glioma like brain melanoma, gastric and testicular cancer. Anybody can ask questions for each presentation. For example, let's say, the endometrial group is presenting. And then, like the kidney group leads to questions. So so. yeah, yeah, and actually, so, so would to sign up for the cancers. This assignment actually has 2 parts the first will be the in class discussion, which will take place on February twenty-seventh. And it's a really interesting paper by Gilbert Welch, who's based on women's hospital and Doctor Day thinking about how does cancer screening save lives? You'll have 90 min. to write a very short 500 word letter to the editor in response to this article. You can work on your own, or if you want to work with a total of 3 authors altogether, including yourself, that will count for 15. And then the final quiz. You can use class notes, presentations any related merit materials, but it really should be your own work. We don't want tools such as chat Gbt, or growerly, and using text that's produced by this as part of this course. If you are going to be using it, you should let us know it should be appropriately cited, as it's as you should, otherwise it would be considered plagiarism. So any any questions about the assignments? Or oh, I should say also regarding the use of zoom The lecture will give a brief overview of the pathology and biology of cancer. We'll be talking also about some of the key molecular and genetic features. The word cancer comes from the Greek word carcinoma for for crab. Prostate is the most commonly diagnosed cancer in in men or people with prostate in a hundred countries around the world. In including of the United States, however, the structures adjacent to the prostate the seminal vessels. You almost never see a primary cancer rising there. Cancer epidemiology is a course on cancer epidemiology. Learn more about the different types of cancers and the different factors that are involved. Learn about prevention, prognosis and treatment options for each type. Think about patterns of cancer occurring in different populations, how we might identify the causes and opportunities for prevented. Study design web. So, thinking about the methods that we use. You know, there's there's you. In 1761, Dr. John Hill wrote a pamphlet cautioning against the moderate use of snuff. Alexander Pope and his essay on man said, the proper study of mankind is man. As an epidemiologist, I think we're very interested in understanding what are the causes of cancer The first real epidemiology study was in 1912 looking at a case control study of tobacco and lung cancer. But it was in 1950 s. That the epidemiology really solidified one of the big cohort studies. The National Cancer Institute was established in 1,937. It was 1964 before the Us. Surgeon General first came out with its report on smoking and cancer. Warning labels appeared on cigarettes in the United States in 1965. An Italian doctor, Ramazini, who made the following observation, in a population of nuns they seem to be immune from developing cervical cancer, but had a higher than expected risk of breast cancer. What factors might underlie this association? Once you turn to your neighbor for exposure to human papilloma virus, either 16 or 18 is a necessary, although not sufficient cause of cervical cancer. There'll be a great discussion about reproductive factors, including a pregnancy. Harold Zarhausen was a virologist, who had originally hypothesized back in 90 s. 74, that cervical cancer might have a a viral ideology. He initially, he didn't. He thought it was related to herpes virus, too. But what he did was There's a pre, the established, pre malignant lesion. That with a high risk of going on to cancer. So you can. actually, instead of detecting the cancer itself, you can detect the the pre malignancy lesion and take it out. One of the first strong links between occupation and a cancer was made in 1775. Percival Pot was studying children who work chimneys sweep so they would go in down the chimneys and clean with a brush. Chimney sweeps were exposed to a pyre in the suit, leading to an excess risk of scroll cancers. The suit wasn't identified until another 60 years later. It was actually benzo. About 30% of cancer incidence is due to inherited genetic causes. The one of the first descriptions of family history of cancer was a was done by Paul Broca. So the the first matriarch of the family was Mrs. D. Clara: Does having a family history mean that it's a genetic cause or not? Does it have to? So why or why not? What's your thinking when you're hearing family history. Clara: What might be the reason that your family history is. In 1915 to 1929, women were recruited to paint the dials of watches so that they would glow in the dark. One of the first watch factories was in Waltham, Massachusetts. Hannah and Weiberg talk about the link between radiation and bone cancers. Robert Weinberg, a biologist physician, wrote a piece about the importance of cancer prevention. We'll talk about what these are the sort of the the defining features of cancer. One in 2 people in the U.S. will develop cancer. There's certain people who seem to be immune from cancer. Do you think really, that everybody would develop cancer if we lived to 100 2,130 years, or do you think we really are? autopsy studies are looking at the tissues of people who die of many different causes other than cancer to see if you can see evidence of cancer. And so it goes to this idea of sort of what we call almost like pseudo cancer. It has all the features of what you say is cancer. But it Almost all of the I would say, for 80, almost all, all the people over a have certain kinds of these mutations. Whether or not it is frank cancer. It's debatable on the type of how you define cancer. All tumors that are cancer have is that they're invasive and benign tumors are often sort of encapsulated in themselves, and they're not invasive into the adjacent tissue. Malignant humans are often poorly differentiated, or e. Malignant tumors don't always metastasize, but they often or can. Malignant tumors or cancer are are really much more aggressive, they often can cause death. Can a benign tumor ever cause death? Can you think of an example? If it does. As cancer grows it needs its own blood supply called angiogenesis to both get additional nutrients, but also take away waste. And then ultimately, if you have a cancer growing in the breast tissue that then can metastasize it has to be able to set up in a different environment Dysplasia is a benign enlargement of the prostate. In contrast to hyperplasia, you can start to see pre malignant changes. The goal would be to actually identify those before cancer occurs. Carcinoma inside. 2 are malignant cells that have all the features, otherwise of cancer, except for the invasiveness components. Lower stage, it's not considered cancer. Even with Cervix, the insight to it still has not invaded into the adjacent tissue. So that but it's still the risk that it will is high. So it's really concerning you still wanna remove it? There's different risk of cancer occurring, depending on the type of poly. Once cancer is occurring, the way that it gets described is based on where the tissue originated from. And actually, so, and trained actually as a pathologist before studying epidemiology. Sarcoma is a malignant tumor that is, arises from mesenchymal tissues. Osircoma carcinoma is malignant tissue that occurs in epithelial organs. Malignant tumors that derive from melanos sites is melanoma. The vast majority of lung cancer is carcinoma meaning it's originating from epithelial tissues. But then you can break down the carcinoma into those that are small cell :08 and versus non small cell lung cancer. And so this is a figure looking at the association between the number of cigarettes Smokers have a range of about 8 to probably 20 fold increased risk in those people who are smoking 30 or more cigarettes. The strongest association are for cancers that are squamous cell. The association of risk factors and cancers, we're starting to realize may differ based on things like the histology of of the tumor, and we'll talk about some examples. I think, colorectal cancer. It also may be not onlyhistology of meaning how it looks under the microscope Small cell:21 can serve, whereas in. :35 especially when it's not :40 the. small cell present within the central area of the one field, whereas and also we don't really operate how we treat them. Small cell:59 cause it doesn't help. Cancers seem to metastasize to different parts of the body. Prostate is primary side of metastasis to the bone, and you can see here other sites, common sites of metastasi. histologic grade, which is what the pattern of differentiation looks like, and you can sort of see things that are well differentiated. As they get less and less looking like the original tissue of origin, th they're they're thought to be more aggressive terms of prognosis. Staging of cancer is the staging of cancer, and for many different cancers. We use a system called T and M to define is the cancer still localized :00 to the original tissue of origin. And then finally, metastasis to more distant organs. We're really starting to see with breast cancer and heather lies, and we'll talk about this in some detail. Not all risk factors are the same for cancers that have the estrogen receptor present in the tumors versus those are absent. Not all cancers are occurring through simply through mutations. There can be effects that are not through mutations that are on the Rna level quantity. Some risk factors may be acting, not by doing damage to DNA, but actually by impacting something called epigenetics. There's a couple of different ways in which genes and our DNA can be altered. You could get an altered copy from from your parents, so it can be inherited through the germline. You can also get alterations that can lead to what we call somatic damage or changes to to DNA after One of the twins spent a year in space, while the other twin, who was also an astronaut, was on the ground. They found big differences in the Gene expression of 800 genes that seem to be due to epigenetic modifications. epigenetics is something that is :29 kind of potentially modifiable, whereas, like a DNA mutation is, unless you can get rid of that mutation through program cell death, or something like that is not modifiable. 99.6% of our inherited genome is the same. About one in 400 base pairs vary between all of us, and whether some of those are associated with cancer or not. Some of the individual genes are different, and they do contribute, but some of them don't. There's a great course, I think, on genetic epidemiology. If people are interested in getting more depth on some of the underlying genetic causes of disease. So if you're interested, we'll talk about the role of inherited genetic factors. Tumor repressors are genes that tell cells not to grow without a gross stimuli being present. Mutations in these DNA repair genes can make them less effective in identifying tumors. There's a theory about this to hit hypothesis in in cancer. That it takes. 2 alterations :51 in the chromos like. So you have. 2 chromosomes so you need to have a mutation in both in order for cancer to occur. You really have to get end up getting 2 mutagenic hits in the same cell in order for cancer to occur. So again, this is just sort of an overview of some of the key concepts in :02 kind of the path of biology, of cancer. We're really excited to have you all here feel free to email, any of us make sure if if anybody is having any trouble accessing the Harvard canvas page. And we otherwise we'll see you on Thursday.

The question is, which of the following is not true about breast cancer. You can either join by the web you can join by text, or there's also a QR Code. And it looks like we have 15 people who have responded for people just coming in. Dr. Eliason: 51% of tumors arise in the left breast versus the right breast. Excess body weight early in life is a risk factor for breast cancer. If anybody wants more time, just raise your hand. Harvard students will have their first assignment next Thursday. It will be a study using the all of Us research program to look at the association between air quality and cancer risk. The assignment will be due by the end of the day. How do you approach reviewing a a paper for a journal article? Usually you wanna look through and think about the study design. Is the hypothesis sound? Have they taken, undertaken the study with with rigor? And so that the results? Starting at 50'clock today, start thinking about which of these cancer sites you'd like to take part in. And remember, there's 2 parts to this. There's gonna be an individual. Write up on the descriptive epidemiology of that cancer. And then, you're gonna have a 50'clock today go to Harvard canvas and sign up self. Select for one of the cancers any questions on either of the assignments. Yeah, is it 5 or exactly. Any other questions. When you think about family history. of in doing an epidemiology study. How might you collect information on family history? What are some thoughts on where you might get that kind of information? If you just wanna collect family history, you might wanna ask not only did has anybody in your family had breast cancer, prostate cancer, pancreatic cancer, etc. You might also wanna know if they died. And then, with with the advent of of genetic testing, or even things The study looked at 10,000 people ages 30 to 45 at the start of the study. Some of their family might not be old enough to have undisturbed cancer. So there's 2 kind of interesting things with that. Maybe with a cohort study. In a cohort study would be non differential right? So they would be as likely to over and underreport it. So underestimate the genetic risk, because people are dying from other things. Are there shared genes between those 2 causes of or the other way which would be interesting. In Scandinavia, where they're able to track cancer, hospitalization, death in the entire population. These things are required by law to be registered into these national databases. They were able to create something called the multigenerational Register. Study included 2.2 million women who are leading living in Sweden. 54 0 cases of breast cancer occurred, and then these are the relative risk breast cancer in these women. If you have 2 sisters, a mother, sister, and even a stronger with mother and brother. If you have more family members that have the cancer, it might be more indicative that family history isn't just that shared environment that we talked about, but also, maybe more due to genetic factors. One interesting epidemiologic approach is to look at twins. There are 2 main types of twins, others, these on identical or monozygotic twins who share in theory 100% of their inherited genome. Then you have 50% on average share genetic factors in the fraternal twins or the dizygotic twins twins. Sweden built a registry of over 200,000 twin pairs from the Scandinavian countries. They can follow up these cohorts for decades and see who develops cancer. And so this is a plot of the age looking at age of diagnosis on the X axis, and then cumulative risk of cancer on the If your dysa got a twin, the likelihood that you also would develop cancer during your lifetime is closer to 40%. And then, if you're an identical twin and your twin pair developed some form of cancer, your own risk, was closer to about 46%. So sort of again, Genetic factors have a small role, but much more so environmental and lifestyle factors play a role and colorectal cancer. In contrast, prostate cancer. and then melanoma seem to have these very strong genetic factors. About 99.6% of the inherited genome is similar across everybody in the room. Single nucleotide polymorphism changes just a single variant change in the DNA. Most genetic variants have very, very small effects on diseases. You have very rare variants that cause disease in a Mendelian fashion. If you have the very rare, it's a very high likelihood that you're gonna get the disease. About 5 to 10% of cancers that have an inherited cause are due to these family syndromes. The more rare the variants are the stronger the effect size is, and then more common variance tend to have very modest to low effect sizes. There can be many cases in a family with the same type of cancer. urring is very, very high, and it gets passed from generation to generation. Other features of hereditary cancer syndromes are cancers occurring in the sex not usually affected. The lifer-mini syndrome was really identified by Doctors Lien formini back in 1,969. They were really interested in the Gene, p. 53 which plays a broad role in cell growth in cell cycle arrest in DN. So they're they're playing a role in the development A repair-related mechanisms. It can play a role in apoptosis which is basically programmed cell death, and it can eliminate any damage cells. It plays a really important role in cellular growth as well as making sure it gets rid of any bad. There are people in which their germ line has a mutation already. All you need is one more in order for cancer to be occurring. While you can't probably prevention, for these families may be hard. These aren't populations that you'd wanna do muc Elephants have 40% more cells than humans. Elephant cancer mortality is between 10 and 25% in 4.8 years. Elephants are on more intensive surveillance at much younger ages. lynch syndrome occurs when there's inherited mutations in a type of DNA repair called mismatch repair genes. This leads to a syndrome hereditary non polyposis, colorectal cancer and as as you were saying, egg what you can see here. The lifetime risk for indonesal cancer about 60% compared to about 2% in the population. Also, elevated risks of stomach, ovarian cancer, and some other cancers as well. The Manhattan plot plots the number of genetic variants associated with cancer. It looks at millions of single nucleotide polymorphisms. Usually you set your P value fairly, conservatively at 10 to the minus 8 here. The individual effect of these variants, though, is really small. So the relative risk, if you looked, might be 1.1 1.2. The question is, well, maybe if one variant so you're not getting much of an effect. What if you took all Polygenic risk score looks at people who have the highest genetic risk. You can really start to see big differences in risk prediction. Could you use this like for early detection of cancer, for example. There are on this plot, 450 unique genetic variants, with a P. Value greater than 10 to the minus eighth. And then you make a simple score, and for each person say, Do you have it or not? Yes or no? Prostate and melanoma were the 2 cancers in the twin studies as well as in family based studies that have the strongest inherited genetic component. Some people have 50 variants or 100 variants. Depending on how many variants you have, you can create these polygenic risk scores. Ji-wa snips are being used clinically in these kind of cancer syndromes. Do we use them, and do they copy? Not yet. But people are doing that to say, could you use this as part of an early detection strategy? An incidence rate is the number of cases of cancer in the population. A mortality rate is a number of cancer deaths. A fatality rate is number of people who have died of cancer. An interest rate is number of new cases. There's a difference between cancer deaths and fatality. Can you think of a a cancer when the cancer has a very low incidence rate, but a high fatality? Exactly right? When you look at the vitality, so what happens in people who have the cancer, it can look pretty pretty awful. So that's an example where the mortality is telling you something a little bit different. It's really a population level statistic versus the fatality. LZ: Have you ever heard of the concept of years of life lost? LZ: Here's a life lost that's close. That's that's Dali's or disability adjusted life here. LZ. lified formula, incidence, times duration. For cancers like prostate cancer, which the age at which people were dying might be 75, 80, even though the mortality might be high. Loss is not as much because you're dying around this time you would have died anyway. This is the crude incidence rate per 100,000 people of cancer in different countries. The darker the blue, the higher the incidence rate. The lighter, theblue, the lower the incidence rates. Age standardization is a way to look at the age distribution of people in different countries. In countries that are considered to be low and medium resource, countries versus those that are high resource. Every country is going to have this same distribution of age in it. But I'm taking the actual rates of cancer in the individual countries for those ages. And then I'm getting an adjusted rate. Does that make sense? The prostate cancer mortality rate in white men is 28.7, and in black men to be 28.9. mortality from prostate cancer increases really exponentially with age, so that the rates are about 100 times higher in men 65, and older compared to younger men. The question is really is that we don't want it to be about age differences, right? Because right now, on average, the black men in the whole population are younger than the white men. So we wanna say, is there a difference? A racial difference? We see that There's such a strong association between age and prostate cancer mortality rates. So even if the mortality rate in each of the age groups was sort of similar, you're gonna upweight. What's happening in the black men? What's happened in the white men? This is a hypothetical example of looking at the association between infection with HIV :46 and the risk of Non Hodgson lymphoma. So in this case, you'd start with a group of individuals where nobody had cancer at the start of follow up. Case control studies are often done in cancer, particularly when cancers are rare. You're gonna have to have such a large cohort and follow people for sufficiently long enough to be able to have enough cancers cases in in your cohort. There's still some cancers where the the incidence rate is so low in that population that's not really sufficient. In that case, what you could do instead is identify your cases in some way. And sample people who don't have the cancer. And then assess the exposure. The big focus is really on relative measures. What's the relative risk of cancer in the exposed group versus unexposed group? You can also think about absolute measures of a factor of risk differences. You're taking the prevalence, not in the cases, but in the full population. So the the attributable like none of the cases there can be attributed to the exposure. And this is really driven by the strength of the association of so something like lung cancer and smoking. The relative risk estimate is much smaller. What's different here is in the population. Trivial fraction is :41 that you're looking at a different prevalence of exposure. Smoking was probably the one that was the strongest cause. The the association between smoking and lung cancer is probably a relative risk of about 10 to 20. Some people who have regressive forms of cancer might lose a little bit of weight before the cancer diagnosis. There was no association between physical activity and lung cancer that the observed dissociation you had was completely due to confounded by smoking. ncer is a big example where you actually have weight loss before diagnosis. And then, of course, with smoking you might look like you have a lean body The study looked at the association between coffee consumption and pancreatic cancer. The study was a hospital-based case control study. The relative risk of pancreatic can was found to be higher than for other cancers. If you drank one to 2 cups of coffee per day was 1.8, meaning an 80% higher risk compared to no drinking coffee. It went as high as 2.7 cups per day, and they adjusted for cigarette smoking, which :33 they thought could be an important confounder. It could be a couple of things. It could be sort of recall bias in a way that, remember, comes to the other points or the pancreatic cancer is really ruminating about their causes. Maybe you're feeling sick. Or maybe you're you're having some gi symptoms. Remember the odds ratio essentially. The way you're calculating is what's the odds of exposure in the of the exposure, in the cases :14. That's sort of one way to think about the odds ratios. Coffee and pancreatic cancer. Ad been drinking less because they were feeling ill :05 in this case for the cases that would actually then lower the odds. Ratio right? But the point that you just raised, which is a great one is. :29 look at where they got the controls from Dr. Jovanucci did a study that he did as a student. He wanted to kind of test a hypothesis out there that consumption of dietary fat was associated with an increased risk of breast cancer. He did this really cool design, which was, he had access to a cohort of nurses. The study was called the nurses health Study. There was a food frequency questionnaire that was asked and collected all sorts of information about the types of food someone ate. The study followed people forward for breast cancer. The study looked at 2 different approaches to the risk of breast cancer. The first was prospective cohort analysis, and the other was case-controlled techno analysis. The researchers found a differential type of bias in the cohort of nurses. There might be this connection between dietary, fat and breast cancer risk. So it could be a concern of recall bias in one population. And, as you said, because they're nurses and more engaged in the healthcare system. In some cancer patients, when the cancer is more aggressive, can actually lead to weight loss. Brian Wolfen is gonna come talk pancreatic cancer, how they're taking reverse causation and turning it into an early detection opportunity. People who eat a healthy diet and engage in physical activity and maybe don't smoke are probably the ones more likely to get cancer screening. That's something that's gonna be highlighted across different lectures. The office hour is going to be on :58 next next Thursday after class, and it will be recorded so if people can't make it. Remember, at 50'clock today :18 the Harvard canvas is gonna open. The journal of the National Cancer Institute, just came out recently with an announcement. The key difference with the population attributable is, instead, you're using the prevalence of the exposure in the full population, which often can be lower. So, for example, if you were looking at, say, smoking and lung cancer

An announcement about the groups for the descriptive Ethi project. Also, it's great if you guys can start meeting with your groups and sort of just introducing yourselves and then I on the on the description on Harvard campus. And then on Thursday we'll we'll make a announcement. There's an annual potato fight in Spain, involving hundreds of thousands of tomatoes. There's more lycopene bioavail in raw tomatoes than those cooked in olive oil. The concentration of Lycopene in the prostate is much higher than other tissues in the body. When people eat a lot of cooked tomato products lycopene concentrates in the process at very high levels. It's also very interesting when people are exposed to heavy metals, those heavy metals accumulate in the prostate. There's a small town in Spain which, right after the tomato harvest, they it started as a food fight, and now every year. It's it's like an attraction w Time in cancer, epidemiology, studies. We know for many, many types of cancers. It actually can be years, if not decades. It varies for the type of a cancer and also varies for type of exposure that it is. There's sort of 2 types of exposures that we think about initiators and promoters. The initiators are those kind of factors that probably do damage to DNA. It's not submission for cancer to occur. You need things along the way that are promoting. The level of adiposity that one has as a child or during adolescence, seems to be actually associated with a lower risk of premedibosal breast cancer. Also, as I mentioned, prostate cancer, where whereas it's associated with an increased risk of breast cancer for When a child is born with a prostate, it's still about the size of a grain of rice. It doesn't really start going through full growth until puberty and for breast tissue. Height is associated strongly with an increased risk of many, many different types of cancers. Analysis in radiation and cancer tried to understand what is the susceptibility of different tissues to radiation. Depending on age. This is specifically looking at a range of studies that looked at different types of exposure to radiation and risk of breast cancer. Study looked at people who were exposed to radiation during the bombing of Hiroshima and Nagasaki. Y-axis is that, and then on the X axis is the age of exposure, and what you can see is the lifespan study was is a follow up. Fluoroscopes were almost like real time movies of using radiation. Women were getting very high doses of radiation if they had Tb and had undergone fluoroscopy. So again, these were women at these ages, so not quite as strong with excess risk. The latency period is when we first measured have information on when the exposure occurred. It's a period of time between when the first initiation happens and when cancer occurs. And so this is where we get this idea that there's about a 20 year lag between smoking initiation and lung cancer. There was a randomized trial of low dose aspirin and cancer risk, and this was after long term, follow up of about 18 years. So the incidence is higher at the end of 18 years of follow-up of compared to aspen. The study looked at full weight, consumption, and the risk of colorectal cancer. There's information on diet every 4 years, and so that allowed the researchers to estimate ev. In order to try to understand the impact of when folate might be important in terms of risk of cancer, they undertake undertook a number of different analyses. And what was interesting to see. was that the strongest association of Foli intake being associated with a lower risk of colorectal cancer, was in latency is this concept of how much time between when the exposure first started. and the time when the cancer was actually diagnosed. So for Folate, you really needed to look back at what someone was doing 12 or 16 years before the diagnosis in order to see this inverse Association. When they follow people longer, that's when they start to see this divergence. You're starting to see the time between that initial exposure and cancer risk of 10 years. globally, over 19 million new cancer cases are diagnosed. It's more common in men than in women and about 10 million cancer deaths occur each year. But there's considerable variability across the globe in the incidence in mortality rates from cancer. This is based on data from 2,020. se I think if you looked now, I think COVID-19 deaths would would really probably rank somewhere, third or fourth, I would guess. There's variability in the incidence and mortality where they're happening across the globe. The total number of new cases and number of deaths from cancer is expected to increase so much in 20 years. There's parts of the world where the aging of the population is happening much faster than it is in in the Us. We even lost years of life recently. But you're right. I think There's populations where some types of screening have generally not been done that may be starting to screen. Maybe it could be diagnosis methods improved. And you're gonna be diagnosing something called what we call pseudo disease. Parts of Southern Europe, for example, that used to have healthier Mediterranean cell diet that are leaning more towards Western style diet. You're also seeing that epidemiologic transition in other parts of, say, in Africa. The American Cancer Society puts out statistics each year. It's suspected that about 2 million people are gonna be diagnosed with cancer in the United States. Ed was just recently awarded a research professor at the American Cancer Society. Lifetime probability of cancer is about 39% women and 41% men. There's some parts of the world where they capture mortality data pretty well, but not in cancer incidents. In Scandinavia, it's actually mandated by law that all cancer diagnoses are reported at International Agency for Research on cancer. Puts together. national databases together. You're gonna use it for your project. The cancer atlas has really great graphics. And then in terms of data from the United States American Cancer Society. Most commonly diagnosed cancer is breast cancer, prostate cancer. lung cancer is third, colorectal cancer, fourth, cervical cancer ranks. Fifth, and I think this is really unfortunate. Given how much we know about prevention of cervical cancer through through screening right? Lung cancer, mortality, colorectal cancer. Many of the registers report melanoma. But don't report other types, squamous or Basil so and mo. They're probably very high incidence, but not high mortality. Lung cancer rings, first, breast cancer, mortality rings, second, colorectal cancer, liver cancer. liver cancer was a little bit lower here, but because it's so highly fatal in terms of mortality rates per 100,000. Pancreatic cancer was something someone mentioned in terms of mortality. It's alarmingly high in the United States for mortality it's become for men the fourth leading cause of cancer, death. Smoking cessation in men probably started in the late. mid to late. What about women? What are you saying in terms of the timing of when the increase happened? And then, when the decrease happened? What do you think the reasons are? There's a large difference in both incidence and mortality of cancer, by sex. The one cancer that's higher in women than it is in men is thyroid cancer. Smoking is a risk factor for many cancers, and in many populations men are more likely to smoke. There's been a lot of research into try to understand what other factors might be explaining this excess risk. So I know some of you were in my cancer course. So magic trick the whole course. I'll try to cover today. The assessment is is so important, you know, smoking and cancer. We think we can assess smoking pretty well, but the diet is very difficult to assess. And actually, I'll talk about that mostly on on Thursday but keep that in mind. There's micro nutrients vitamins, minerals, calcium and then there's phytochemicals. Chemicals are things like that you can get. For example, fruits and vegetables are antioxidants. They're technically not nutrients. And I think fiber is in there, too. There are a lot of things that you know. Obviously you don't want mercury, but it gets into fish, for example. II should also put like additives, forexample, artificial sweeteners. I mean, it's really important. There was a lot of interest in diet and cancer. Most of the evidence at the time were like animal studies, mechanistic kind of studies. Case control studies began to emerge, and then cohort and randomized trials came a little bit later. colon cancer rates went from about fivefold lower to twice as high, particularly men. Smoking alcohol could contribute in part to to the men but smoking and alcohol is won't contribute for many to cancers in in Japan. There's a very strong correlation between fat intake and breast cancer mortality. I wouldn't for a causality, but it again. I actually 1975. Now, at the time, actually, there was people really did jump onto. Oh, it must be fat in 1, There are thousands of potential compounds that may be beneficial case control studies particularly indicated inverse associations with fruit and vegetable. It just shows that there's something probably related somewhat to diet accounting for this. There are lots of compounds concentrated in certain foods that have all these effects, like our OS. Scavenging is like reactive oxidants species. So that's like antioxidants. They affect lots of things in the carcinogenic process. Dietary fats. mpletely block blood vessel growth and tumors. So these are very interesting. Now, you know whether they're important in people is questionable. 30% of cancers all cancer mortality would be prevented, preventable if everybody like and stop smoking or or didn't smoke. And of course there's a latency issue, too. So have maybe people did smoke for 20 years, the last one. The US. had this very high estimate for diet. :03 35%, but also a very wide range. :12 Now :17 these, how do they come up with these estimates? :19 th, they were. There's very little direct data. A large number of cancers are preventable and they attributed a lot to diet. It may be possible to reduce us cancer death rates by practic practicable dietary means by as much as 35. The parts that contribute to it are uncertain in the extreme. Cancer may be affected by things like nutrition. Some of it may may be this early life exposure, like affecting the agent, monarchy or height, and that might be related to things like growth. One statement that they made here that I think, really had a big impact on the field. It says any of the punitively protected nontoxic vitamins trace elements, micronutrients protease inhibitors or antioxidants that finish up in the top 12 might just be testable. If you're focusing on a micronutrient why not do a randomized trial. Right? That's you'd get a very definitive answer. It's probably would make more s There was a lot of interest. There's not much interest nowadays. It's just a compound like that may have anti-cancer effects. That's part of all the micronutrients in that. randomized trials are considered most reliable type of evidence when you could do it. Most of the evidence is from case control and cohort studies. But there are issues like. latency is one of the issues that we'll talk about. There's almost no way around it. If you're looking at, you know, diet :33 and cancer life course, eating like fruits and vegetables like over your entire life. Does that have an impact on cancer that that might be harder to do a randomized trial. Double blinded study is feasible in most cases for diet and cancer. It's hard sometimes to do like a placebo control. You can't ignore that information for ethical reasons. For example, the effect can be over. E ecologic data do inform sometimes on dietary hypotheses, but usually don't form drug therapies. You have a new drug tested before. Not all aspects of diet people in the pill. You you can only do a micronutrient type of stuff. There are potential issues in trials. The study isn't large enough, or the adherence is low. Even if you're just focusing on something, you can actually put in a pill like a vitamin. When you look at colon cancer and years of multivitamin use of. to cancer. :24 you see, like not much going on, certainly, after one to 4 years, and then perhaps :31 suggested a not significant reduction like 5 to 14 years, but then a clear lower risk. If you have something that only protects against initiation but doesn't affect promotion, it's going to be a while to see an effect. The ones, if you can look, I mean, this may be hard to do. I mean you can do it sometimes like, for example, colonoscopy. Even if you for 55 year old, like, if you prevent initiation. Yeah, maybe you'll prevent a cancer like when you're 65, or 70. But you're not going to prevent a. cancer that they're going to have at age 60. So so that's that's a I think there is some evidence for for childhood cancer. Like I think II don't maybe lower life, or someone knows better like for some Leukimius. I, for instance, the genetic makeup would have less stress and less. The group that starts with twice as many initiated cells probably is going to have twice the risk of cancer. It's hard for some people to understand this, because they see? Well, the cancer happened like at age 70. There is a inverse association, right? So starting from low calcium intake as you go high, the risk gets lower, and then it levels off right? :56 Another issue is, you know, I think Dr. Sam will talk about this more. In the Women's health initiative, like they assessed calcium and the women in the trial were already taking, but on average, 1,150 milligrams of calcium. So they were getting at least, let's say, like 12, :33 you know, up to 1,500 People already have a calcium intake level which can affect the trial. If it's done in a low calcium population, you're stuck like the trial might see a benefit, because you're studying this. But if it's if your calcium is already high. Vitamin e :51 and beta carotene :21 which is one of the precursors for Vitamin a. Alpha Tacophile and beta Carotene have antioxidant properties. So they said, like, Wow, maybe all this benefit of like fruits and vegetables, or a lot of it Long-term smokers in Finland have high rates of lung cancer. Vitamin e alpha taco, or Beta and Beta and see if it's protective. It seems like no difference. It's almost exactly the same. Men who got Beta Keratin had more lung cancer than the men who got placebo. Alfred teferall didn't work prevent lyme cancer. This truck Beta Carotene is not beneficial. It's actually bad fuel. Fruits and vegetables associated with with some cancers. Lower risk of some cancers in case control studies, fruits and vegetables are high in antioxidants. High dose of Beta Carotene was much higher than you would ever see under the diet. Antioxidants Beta Carotene and Alpha Cartherol, Antioxidants there were actually just. :06 but were really interested at the time, you know, because people were just learning about vitamin a and vitamin e. A lot of these men already have these advanced free cancerous lesions more or lung cancer risk with 5 years. atural diets and extremely heavy lifelong smokers. The trial may have asked an interesting question, but has it really addressed the top

You should be able to see your group full lock after today after we put people in a, you didn't sign up death. 4. That are looking for other people are suffocial cancer and ovarian cancer. Both of which are fascinating cancers. Oh, and then this is a last in There's been some hypotheses in the literature around the role of sex halo, things like estrogen and androgens. So which of these? Do you think is a proxy for greater exposure to androgen such as testosterone during, while you're a neuter. Students thought that exposure to DES during pregnancy and this was given to present many decades ago to prevent complications during pregnancy. Actually, interesting DES exposure has been linked to more rare cancers in the offspring. My ratio, I mean I don't know if this is HIPAA or not? You're second before, meaning I had much lower exposure to androgens and higher exposure to estrogen. My birthday, surprisingly actually is associated with lower levels of testosterone that thought to be higher levels of estrogen during This is more to help you like assess dietary nutritional studies throughout the course. For specific topics, you'll get more specific knowledge of the nutrition cancer association, particularly for example in colon cancer. So I won't get into a lot of specifics, but be kind of broad Bial markers are not you know, there are few biomarkers that tell you exactly what somebody is eating, but they're like indirect. If you eat lots of fruits and vegetables, your blood beta carotene levels will be highs. And then there are things like iPhone apps, like, Diet is not like a simple exposure. Like, you know, number of cigarettes per day. And the later I'll talk about like an energy balance. There's no really good dietary assessment to that. You have to measure. things almost perfectly to get energy balance. So the balance in minus out and neither one of those are really that feasible in epidemiologic studies. 50 questionnaires are currently the best. for micronutrients. Beta carotene and carcinogens can be useful markers. RCTs could be used to test for carcinogens and contaminants. There are lots of factors, but it gives you a pretty good indicator. Longer-term memory is sometimes even better than short- term memory. Short-term memories are sometimes better than long-term. People often ask how they remember over the past year. But the longer term memory is often better. Long-term memories are what you really want for cancer studies. Dr. Willett led some of the studies and, you know, he did a lot to show that nutrition can be assessed in epilogic studies. Study looked at 173 women across the U.S. for 4 weeks. The data was collected from a food frequency questionnaire and 4 one week diet records. A perfect correlation would be 1.0. On average, the data was about point 6 4. There's actually a lot of measurement error in the lab of getting like the exact energy of expenditure for example. Some are better than others in Lodocanas that here are pretty close. Protein is more restricted in the population. So in a sense it's not so much that the absolute measure is worse than the others. It's actually that you have less variation. I'm just thinking you might eat more fresh foods and vegetables in the summer. I mean, there is no, I mean, point for me, like point 2 is definitely too low. Point 8 would be. You'll be very happy if you get that in theology for tradition. Personally, I'd say like below point 5 would be problematic. Health professional studies, which is pretty unique, is that there are multiple measures like every 4 years. Some of reports have like 8 or 9 questionnaires over their life. So that kind of, you tend to get Probably better information like more people. The data from the validation study. Which you can kind of use to, adjust your findings in your studies because of the measurement error. People sometimes don't like that, but that's, you know, one way that it's dealt with. Study looked at 626 men a single. That's a 24 h recall, 24.h calls. An FFQ for food for can see questionnaire. And then a single and. 2 weeks of diet records. The correlation, you know, it's about point 7 here. This is the, food frequency process, 2 food flips. 1 7 day diet directed it's actually not much worse than having to. You know, correlation is a little bit lower. The higher the correlation, the better the measurement. For sodium where the diet records are better than the food frequency question for Sodium. sodium varies a lot in foods like, you know, things like folate or protein, potassium. So like you do like the FFQ does miss some of the specificity. Food frequency questionnaire is, like, you know, It's almost like pennies. One of the big, improvements was like optical scanners like you fill in the little bubbles. That made the study very feasible to do in the 1980s. Diet records have been matching like every meal you're bringing a little scale like so yeah there's a also the participant though And then it's also like once. Like the FFQ like you make assumptions like this item has like this much potassium with the diet records. The FFQ is definitely, you know, not as good, but it's not much worse. The WCRF the ICR, that are, they have a, their, their existence is, is to assess nutrition and the cancer. The way they assess the data, so they look at all the like just about any question like you know coffee and colon cancer you know sodium and breast cancer, anything that there's data out there. So they, so the conclusion, so based on the methodologic, you know, In 1990, there was evidence from case control studies pretty consistently that saturated fat and tank is associated with a higher risk of dress cancer. And you can see very, very now a finding for fat and percent energy for fat. The fat composition of the diet from prospective studies were very different from the case control studies which tended to show an association. And now that they're even like, I think this number is probably like 10 times larger. Some people have argued, and I think this was a reasonable argument like maybe 20 years ago, but I don't think it is anymore, that like some of the cohort studies had one measure. And then they had the long term follow-up like 2030 years. So, so some people There's a similar measurement error. The 2, you know, plausible reasons are recall bias, and selection bias. There's for case control studies you see except for prostate you see an inverse association so good diet lower risk. In case control studies, like what people do like to get the cases are relatively easy to identify. And then you have to get controls. And controls like they were done by like random digit dialing because you want to get a random sample. The selection bias is probably even more important than the recall bias. So you can actually show like response rates could be 30, 40%. So I think there's a lot of participate in this study. There are not many things that actually get strong convincing evidence, but there are some items that we'll see that get like probable evidence. And they would still be considered probable, still pretty strong evidence, which that they could actually make recommendations. But, just as a This is just a summary of. the findings and a lot of these. Will be talked about later in the course, but this is a list of what the WCR FX here came up with as related to cancer with strong evidence like probable or convincing. In the second in a few minutes, I'll Dietary patterns are a combination of foods and beverages that constitute an individual's complete dietary intake over time. WCRF is working on a project with them. They're a lot more interested in dietary patterns. It's also, you know, in some ways it reduces like the confounding and just as an example. When you look at a dietary pattern, like let's say for example, you're looking at the effects of a vegan diet. You're not like necessarily saying that they're like like anything specific It's a more general statement. It's probably more conservative than trying to find a whole diet. And it's potentially more beneficial. There are different ways, so what do you mean by dietary pattern? The questionnaire does pretty good at. Picking up a dietary pattern, which to me intuitively kind of makes sense. It's based on the consensus of what's good in one's bad. And, we actually did a validation study. Some people tend to eat a lot of healthy foods and some people less so. The interesting thing is like we're doing this summary for the world's cancer research fund. Some of the dietary patterns do seem robustly associated with total answer. Dietary patterns is like you're integrating information, but I'm almost thinking now it's becoming like there's too many. But I just want to spend, you know, make sure I have some time to get into obesity. There is limited utility for most questions for nutrition and cancer. Case control studies seem to be prom to recall selection bias, making cohorts the most feasible. Established factors outside of energy balance contribution are red process needs fibre whole grains, dairy, calcium. Salesforce. d? You can look at the next slide, don't she? Wait, yeah, that's a good way. Yeah, the bio impedance that they shoot some like electricity and then like if you have more fad I think like you have the conduction is lower. There are 13 cancers that have been established as causally related to a higher BMI. Early life BMI is actually associated to. Protective effectiveness cancer. In post metopausal women like weight gain, for example, it's definitely a risk factor. Excess body weight might account for about 5, maybe 10% of where in Kansas. Obesity related cancers are increasing in in younger population, young adults, and for a Monday obesity related cancers. Among young adults like young onset, colon cancer. You have, like 9 out of the 12 are increasing. In association with increasing adiposity. Obesity is much higher in women than in men, almost like twofold. There are some racial differences in obesity that probably contribute. It's not like maybe the big dominant factor, but it does contribute to some of the differences in cancer rates. In pulse metopausal women and in men most of the estrogens are made in adipose tissue. Body weight, BMI, and estrogen level. There's a linear association. So an estrogen which you'll hear about in future. The main risk factor for gallbladder cancer, which is rare in the US, is golf. Obesity, particularly in men because it's central because it causes like the acid from the stomach to go into the lower part of the esophagus. If the stones are there asympt insulin and inflammation which which are related and I think these are the multiple cancers which I'll talk about. ntinues, but smoking alcohol, the lower part, adeno carcinoma is just the part where you get the reflux. There's even like, Like, Gillian randomization, which I. People familiar with that, 1 billion. People that have genetic variant that makes their insulin levels a way higher than average. Those variants are consistently associated with what some of these cancers, particularly Mendelian randomization studies suggest that it's actually the insulin level that's the causal risk factor. So it's hard to PIN it just to insulin, but I don't increase like 100 other things. insulin, which is, like a marker for cancer risk. The visceral fat is the fat that's internal like around your organs like the mainly digestive organs and the kidneys. Some people have a lot of fat around it work and it's makes it hard if you can find the case. It's hard to measure this real fat, like you can't do it like just like a questionnaire or something you need the more sophisticated measures. :48 And this slide gives you a sense of that. There's definitely a good correlation between waistcoat and visceral fat. You do guess a lot of people that actually have high missile fat. These are factors that increase glycerol fat, you know, bey. Male aging is a very strong association between aging and visceral fat. Lack of exercise, sedentary lifestyle, probably diet, smoking actually. Asian population will tend to have higher higher visceral fat, which is why in some Asian countries like their high rates of diabetes. Most of these studies We're done in either Japan or South Korea. Most people had a DMI less than 25, so we considered that normal. But even within the normal range, it'd be a viceral fat is associated with cancer. Non-smokers have a higher risk of cancer than smokers. High body mass index and weight gain seem to be much stronger risk factors for cancer when you look at non smokers than in smokers. Smoking is often associated with lower BMI. But actually increases visceral fat. For subcutaneous fat, which is most of the fat in your body, it has, little effect, maybe even slightly inverse. Some people use smoking to keep their body weight low. I think BMI just is a bad measure in smokers of visceral fat. But yeah, so, it's still probably better to stop. The WCRF A ICR, to date only have 3 cancers. That date attribute, to lack the frisbee activity or their physical activity contributes a colon, post-menopausal breast, and end of nature. Physical activity is more possibly associated with a lot of cancers. There's 2 cancers, cross state and melanoma, where physical activity has a positive association. Being more active, people reported being more active of a virus. Physically active people are more likely to get PSA tests. Physically active. people have a lower rate of prostate cancer mortality. But you're more likely. to be diagnosed with these. Physical activity is related to obesity related cancers and tobacco related cancer. Some people think it's possible that physical activity is directly protected for lung cancer. There could also be a bias because like light cancer is siated. Smokers who have lung disease like daphragm are actually higher risk for, lung cancer. It's possible, you know, it's conceivable there's some causality, but I think it's most likly related to smoking smokers. Every cancer practically they were physical activity is protected is also a obesity related cancer. Physical act this is a meta-analysis where physical activity. Associated with lower risk of almost every cancer in the digestive system. Physical activity is very important for visceral fat. Up to 300 min per week of moderate intensity or 150 vigorous. You get them also the benefit but you can get more benefit perhaps by going even higher. You can really reduce your visceral fat without having a big impact on your weight change. Once a very active, again, tend to have very low visceral fat. Once they are inactive, still have pretty highness of fat. Liver fats are also probably important for liver cancer. Subcontaneous fat is much more sensitive to physical activity. 's well fat. That basically this is almost like 30 years of my work that I've been thinking about this. Vessel of fat you can be affected by physical activity. These have a big impact on information insulin resistance. Other cancers too, probably contributes to breast and then estrogen is mostly related to subcutaneous fat. Physical activity could still be mediated largely through things like this or or :22 Padded catapults. If you look carefully at the epidemiology of physical activity. And cancer, I think you can explain a lot of it. There's Maybe. At least by population, what people do. Is much more. But resistance would have some of the effects too. We've actually booked that in our data. You see pretty. The correlations with resistance strengthening and Lord

Cancer epitia. Today's question is which of the following cancers has the lowest estimate of heritability. Is it a noma B prostate cancer, c, testicular cancer or D colon cancer? The 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. Colon cancer ends up being the cancer with the lowest estimate of heritability. It's an interesting cancer that way that a lot of times we think of family history as being such a strong genetic susceptibility. A big chunk of is actually due to shared environmental factors and then genetics. "It's really my great pleasure to be here. I remember 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," he says. Colorectal cancer ranks third in both men and women, and also for both incidents and mentality. In the past few decades, as we can see, luckily both incidence and mortality have been declining. There is about 1.1 million Americans living with cancer in 2,016, which represents a 20% increase. 53% of the reduction is likely due to screening. colonoscopy screening has been increasingly used. For colon cancer among young individuals below age 50, there is a growing increase. Improvement also accounts for about 35% of the decline, and this is mainly driven by the reduction in smoking. Treatment consumes the largest of the economic burden for colon cancer. There is also an increase in early onset colored cancer, and specifically in this country some notable demographic differences. 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. There has been an increase after the 1,950 birth cohort. The increase is actually most dramatic for East Asia. There's also a slight increase for the older, for the more recent birth cohort compared to the o. 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. And again, we can see there seems to be an increase after the birth cohort. There is a strong interest in studying early life exposures. This is particularly relevant to early onset cholera. For younger individuals their exposure history is much shorter. The critical period, maybe. is more likely to be in the early life period. Lifestyle medication, environmental exposures can all influence the microbes. If we look at each individual factor, the impact is very small. It's the totality of the environment that really shapes the. vironmental exposures. Colorectal cancer is probably the best characterized cancer molecular. There are 2 major pathways for the development of polaroidal cancer. The natural history evolves from normal epithelium to adenoma and then to cancer. The microsatellite instability pathway is also called a serrated pathway, because it's characterized by the precursor illusion, serrated columns. So for primary prevention, as you must have learned, it's about prevent cancer from occurring. For the risk 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 4 different, like risk factors. 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. Smoking has a long latency period for the smoking effect on colon cancer. So there's roughly, like a thirty-year induction period for smoking. Colloidal cancer is very heterogeneous. There are different pathways. There is data suggesting that cerebral cancers tend to divide more rapidly compared to the conventional cancers. So this has clinical implications because the cancers with the serrated features have been identified. Serrated cancers are more likely to develop after negative colonoscopy. Smoking is so strongly associated with serrated cancers, it really suggests the potential of prevention for individuals who had a negative colonoscope. 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. Sex difference in obesity related cancers has been well documented in the literature. One reason for colon cancer may be related to sex hormones, which I will talk more about that later. The visual ad central obesity may also have some independent effect. Physical activity is also an established protective factor for coloreto cancer. The association is predominantly observed for colon cancer, but also for rectal cancer. But the association is much stronger for digital colon. Digital colon cancer is includes the cancer studies in the like after the the splendid flexure descending, cooling, sigmoid and proximal cooling. There has been a lot of etymology data indicating the molecular and risk factor difference across the subset. Western diet repelling red and processed meat is the strongest risk factor. Right risk is very high for processed meat compared to Rami. For RAM meat there are still some positive associations, although the aftermath is less consistent. 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. In other words, these 3 factors have been pretty well established to have a protective effect on colored cancer. There is a general inverse relationship between binding D levels and cancer risk. A similar inverse association has been observed for calcium. For foli there is a very interesting latency effect. Folate intake of prayer to colorectal cancer diagnosis there is no association. This indicates that it is folate intake that is. decades before that really influenced cancer risk. The supplementation has to happen early. much early in life in order to have to say benefit If we increase the fiber intake for everyone to the recommended level, there can be a substantial public health impact on colonial cancer prevention. As you may have learned from the media, from the literature, tty linear relationship in dietary, fiber intake and cancer. Most of the individual studies for Colon Cancer Prevention have enrolled patients with a history of polyps. Individuals with polyps have already had the carcinogenic process started. So we may have missed the critical time of cancer initiation. The Who is one of the largest intro trial in nutritional studies women's health initiative. Participants already sufficient in their intake for these nutritional factors, for example, for calcium in the Women's Health Initiative. 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 to to to take into account when 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. e Rcts and epidemiologic studies. Anything else that you can think most. Ecologic study can be beneficial or can be helpful for hypothesis generation. Besides diary factors, some medications have also been linked to lower risk of colon cancer. Aspirin is the most established medication. It takes about 10 years to really see a separation between the intervention group and the control group. So again, it highlights the latency effect for aspirin as well. There's also a concern about like aspirin use among other individuals. 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. Aspirin is associated with higher risk of bleeding, particularly gi bleeding. For Cbd there is still recommendation for the high risk. We still don't know why, like what is causing the increase among older individuals. Another medication that has been linked to lower risk of colon cancer is the hormone replacement therapy. And there has been really well documented biological pathways regarding how estrogen may actually protect against colorectal cancer. Microbound is considered as another organ of our human body, and it plays an essential role in both the metabolism, immunity, and also in adaptory absorption. And here, at least, the bacteria that have established to play a role in colon cancer development. 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 that's all for primary prevention. If there are any questions about the risk factor or protective factors In relation to colorectal cancer, incidence, and mortality, we can see that there is a very strong inverse association for both incidence and mortality. This is from the Nordic trial, which was, I think, published in 2,022. The results are much weaker from this trial compared to the observation data. The relative risk is about 0 point 8 2, and for mortality is 0 point 9. As an epidemiologist, how to interpret the observation of universal funding is probably one of the most critical questions. Low participation rate in the innovation group. Crossing over at about 6 years after intervention, I mean, after the start of their trial. Can you guys see some athletes to support from the 2 figures? colonoscopy does not only detect cancer or polyps, it can actually remove the lesions, and it can be both preventive and also to some extent therapeutic. That's why the incidence gets lower over time. So this is pretty commonly observed for conduct, space for clinical trials. The detection bias is actually normally is only observed, for instance, but not for mentality. We wouldn't expect such crossover for mentality, and the fact that the Innovation group had a higher mortality suggests that there's something with the innovation group. The partisan doesn't participate or take less of scope. After many years of the migration, maybe like 5 to 10 years after resignation, their autism rate gets decreased too. So you are seeing this is because the innovation group gets north in time. There may be some variation over time. :10 like maybe, like in the early years there's a higher participation. And then it went down. :34 but I wouldn't expect that's a good point, because the baseline is a recommendation. The study is measuring different things compared to the observational study. Normally for randomized clinical trial, we are interested in efficacy. But in this study, because of the pragmatic design, what they are measuring is effectiveness rather than efficacy. 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. There is a lot of concern about the overuse of screening among healthy, low risk young individuals. There is a potential for personalized or precision prevention, because colonoscopy is very expensive and it is very invasive. 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. There is an increasing number of cancer survivors who are really 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 colon cancer is highly preventable by screening and also by lifestyle modifications. While screening is warranted that lifestyle factors should still be the predominant factors to consider for prevention. There are still a lot of unknowns to be studied for Colonel. tency period for other factors. They are more likely to play a role in the intermediate or even in the late phase of cancer development.

Each year, 15% of incident cancers globally. are attributed to infectious causes. What are some of the major cancers that you think or that you've heard about are associated with an infectious cause? HBV infection is present in an estimate 100% of cervical cancers. It's not sufficient to cause cancer. There's other factors that help to progress it, but it certainly is an infectious ideology. I think there had been a misconception that boys would not get HPV related cancers. So gastric cancers have an important ideologic cause primarily H pylori. So again, as I mentioned with cervix nearly a hundred percent attributable to HPV. The proportion that's attributed to infections globally is about 77%, but in different parts of the world different because of the problems of different infections that contribution plays a different role. At the very low end, probably about 4% of all cancers in Australia, New Zealand are thought In sub-Saharan Africa you can see about half of all of the infection related cancers are due to human papilloma virus. In let's say eastern Asia, we have a big proportion that's due to a helicobacter pylori and stomach cancer. And you can sort of I want to talk a little bit about the International Agency for Research on Cancer, which is part of the World Health Organization. They actually have a very formalized process by which they go through and systematically review and classify agents.

There's a hundred 22 different agents based and this is based both on experimental studies, animal studies, and epidemiologic studies where the evidence is felt to be sufficient to classify to carcin to humans. And a number of the agents are actually infections. Epstein bar virus was first discovered because of its association with burkets, lymphoma, but it's now been shown to have group one evidence that's associated with Don Hodges's symphoma. Colleen and Michelle are the breakout rooms open. I'm gonna open them right now. Take a about a couple minutes, go to your breakout rooms. And then we'll come back together. There may be other host components that are required to be present in order for EBV to work. That's why you have a bunch of other variables that have been found to be personal kicking, there's just still a lot of. Investigations that can be. Done to better understand the TBV as you said is sufficient, but it's required but not sufficient for the endemic form. It's mainly we see it in kids in Africa that present with large stomach so it's also focuses on a specific population. Epstein-barr virus also is a cause for mononucleosis. Study looked at the association between Epstein bar virus and the risk of Hodgkins and Foma and the timing of it. In the first 4 years after mononucleosis, the risk of Hutchins and Foma goes up substantially and then starts to decrease. Even 10 years out you're seeing about a 4 fold greater risk. None of them are associated with the virus of the timing of infection. According to the international agency for research on cancer, these infections agents are thought to be cancer associated infections. The first column are the cancers for which there's sufficient evidence. The next column is where there's more limited evidence. There's very good evidence. Of that HIV associated cancers not only Kaposi sarcoma, but lymphoma's and as well as cancers of the cervix, and is, etc. But there's more limited evidence, but there's, you know, it's where there There's thought to be a number of ways in which this might happen. And, and I, I want to bring in the concept that we talked about a couple of classes ago about some factors. That are initiators of a cancer. There are multiple ways in which infections can actually lead to cancer development. immunosuppression can allow other agents in the host to be more damaging than others. We're in order to avoid rejection of a d Onor organ you you suppress the immune system. The relative risk of say 10 or even 50 full greater risk of these cancers in the presence of HPV. And then when we look at other types of infection related cancer, so for example, Epstein bar virus, human, herpes Antiretroviral therapies are reducing immunosuppression in HIV positive individuals. There's been a reduction in the incidence of AIDS to find cancers in the HIV positive population. Some infections are more likely to be cleared. SIP ship sizes is just the number of siblings in your family and birth order is where you are. So thinking about the probability in the age of earlier infection. What do you think if with a greater number of. siblings you have or where you're with a birth order, how might that impact your SIP ship size has been one proxy for just the probability of infection to childhood infections as well as the age of which are infection. Now what about birth order? Do you think? How might that. Play out. There was a study that was done on birth order and citizenship size in relation to the risk of nasopharyngeal cancer. Sweden did a nationwide study, from 1961 to 2,009 and they did sort of a nested case control study. Just tell me if somebody is raising their hands. About age of exposure to Epstein bar virus. And the risk of mononucleosis.

The earlier you're exposed to Epstein bar virus the, the, greater the risk of, mononucleosis was. Now what about Bernasopharyngeal cancer? Maybe the associations are quite as strong, but what do you see here? Something different, The study was done by Hanzo Lafadami and his team, where they linked the pap smears with information are in the Swedish cancer registry to look at 478 cervical cancer cases. And then this is looking at, a. Count a viral load. The higher the number. The greater Do you see a different association between higher and lower viral load? And the odds of. Cervical cancer in this dataset.

For those with the lowest, viral load, you can see the association between HPV 16 and cervical cancer was probably an odds ratio of about 4. And then when you look at the higher spiral titers. You can see that the relative risk is dramatically increased. You can probably fairly safely wait. 4 years, although of course, you know, maybe if you're in this highest group, you'd want to do more active surveillance of this population. So in terms of screening, you can sort of see this difference between what in 4 years versus Pap smears can be used for prevention. Vaccination for hepatitis B virus, which is a major cause of liver cancer, also recommended. What about something like, what do you know about H pylori? There's a number of ways in which we can think about cancer prevention, focused on infections in cancer. Cancers before they become cancer. So identifying those pre malignant lesions. Certain types of infections that we can prevent. Study was trying to get at a little bit about. You know, is there sort of an immediate in terms of early detection and immediate increase in the odds of cervical cancer. Or, is it a slower latency and therefore you might be able to, you might not need to be doing looking every year. The question really is maybe not if we're going to prevent it altogether, but can we prevent? The the viral load or the age at which someone's infected and it's complicated right because Okay. One more question in the chat. The liver is really an essential organ that plays a number of roles from detoxification, metabolism. It says it stores glucogen. As a result, You know, it's exposed. Blood blows through the liver and as a result it can be exposed to many Liver is a common side of metastasis. So I really try to use the word primary liver cancer. There's a number of histologic type the most common of the histologic types is hepatitis cellular carcinoma. I'm also going to be talking about collagenio carcinoma which occurs in This is for liver and intra hepatic bild ducks. This is not metastatic liver cancer. And so what you can see is when we look at both sexes together and this is data for 2022 we have different parts of the world

Each year globally it's a major cause of cancer. There's about 865,000 in cases of primary liver cancer a year. The incidence is much lower in women than it is in that. In 2022, there will be 758,000 cancer deaths that occur, according to the World Health Organisation. The incidence of liver cancer is moderate so the prevalence of people living with the disease is fairly low. Each year it's about 41,000 new cases a primary liver cancer 29,000 deaths estimated in 2,023. 5 years out, about 20% of patient diagnosed with liver cancer, only 20% will be alive. Hepatitis B infection, really is a different type of virus than hepatitis C, hepatitis B is considered to be what's called a DNA virus. The viral DNA can actually directly integrate into human DNA and as I talked about earlier in this lecture, it can actually Most people with hepatitis B will actually clear the infection if they're exposed. And as only if they become chronic carriers of hepatitis B or C that they will be at risk for developing primary liver cancer. Smoking is thought to be that way too, that it both can initiate lung cancers to Hepatitis B was the first of the virus that was found to be associated with primary liver cancer. It preferentially infects hepatitis. Which are the cells that lead to hepatitis cellular carcinoma. Over 300,000 individuals around the world have chronic hepatitis B infection. There's a high prevalence of chronicity in infants who are born to hepatitis B. So the higher the birth order, the earlier you're exposed. The earlier you're exposed, the more like you are to become a chronic carrier. The greater your risk of hepatitis B infection, therefore the greaterYour risk is going to be a primary liver cancer in the future. Chronic. c carrier, you're not getting rid of the virus. So the virus is going to continue to do damage to DNA and it's going to be able to continue. to lead to inflammation. Inflammation and doing more damage. You would really have to do a blood test to show that you positive for hepatitis B and you do it for that hepatitis B surface antigen. That's going to be the best marker to shows that you're chronic carrier of infection. Liver cancer. What as well as controls. If you wanted to show that hepatitis B virus infection was a causal agent. For bimary, hepatocalial cursor. s B biomarkers. Dr. Chakopoulos included. Metastatic liver cancer as well as hospital base controls. In this study. Any thoughts any, what were some of your discussions? We weren't really sure that. The hypothesis was that hepatitis B, virus should not be associated with metastatic. The other cancer if there is an association. When was blood in this study taken in relation to cancer diagnosis? The cancer itself can often influence levels of different biomarkers. So it's something to take into account with this type of case control study. The first column or data looking at the association for primary hepatacella persona on the rig. Hepatitis B surface antigen is a measure of active and chronic infection. There was a suggestion of an elevated risk, but not really as substantial for the hepatitis B surface antigene. Many studies including cohort studies have confirmed this strong positive association. This was a really important cohort analysis of pregnant women in Taiwan. sis in their liver may have reactivated past infection and that's why you're seeing this kind of interesting positive link. The odds ratio for primary liver cancer was 2.2, but in the presence of both high viral load :00 and high surface antigen, you see this strong. ad from the DNA might play a role. The cancer itself is isn't likely to be causing the reactivation of the virus. Hepatitis C, virus is looking globally just at the prevalence. There's now been a number of studies that have established a strong and causal association between hepatitis C infection and the risk of hepatcellular carcinoma. Hepatitis B and hepatitis C infection increases the risk of developing primary liver cancer. The risk is 18 to nineteen-fold greater for those who are positive for both. There are certain types of molds. that grow on corn, nuts, and beans, and particularly warm and humid climates that can produce a toxin called aflatoxin. There's synergy in in terms of increased incidence of hepasolar cursing of having both infections. There was a really interesting study that was done in the Shanghai Men study that we just talked about among 18,000 men. There didn't look like much of an association between aflatoxin in the diet and risk of a patasilo cursor. Aflatoxin was found to increase the risk of hepatito carcinoma by nine-fold in people with a DNA addict for aflatoxin. Aflatoxin can be hard to measure because food now is really global, right? alpha toxin now is considered a group one carcinogen because of its association with a patasalic persona. Alcohol seems to be its own risk factor independent of viruses. In sub-Saharan Africa, a big proportion of hepatitis cellar carcinoma risk can be attributed to hepatitis B. And C virus because the prevalence of the virus is much greater. In contrast, you can start to see things like alcohol, obesity being much bigger risk factors in Western Europe as well All of these things together have a lined in this model of how primary liver cancer, particularly a pascellular carcinoma, develops. All of these major risk factors do damage and lead to chronic inflammation of the liver, which leaves to liver disease. Cirrhosis of the The majority of primary liver cancer is due to clandio carcinoma. The bile ducts are where colonial carcinoma comes from. It was discovered that by consuming raw foods whethth. Liver flicks are considered now a group one carcinogen. These can actually then infect the bile ducts and lead to the development of clandio carcinoma. By cooking fish, it kills the liver flukes and therefore will not lead to cancer forming. infections are a major cause of cancer, but they're also largely preventable. Hepatitis B virus is really interesting as a model of both. risk factors for clen do carcinoma. Liver cirrhosis really seems to be this unifying model understanding the ways in which ideologic factors are leading to cancer. And it includes both viral and non-viral causes and as the prevalence of some of the viral causes is going down. Most patients who get pancreatic cancer, actually close to 90% actually die from the disease. Just email us directly to set up a time to meet that we really just want to talk about the presentation in your risk factor and give any advice we can. Pancreatic cancer has essentially the highest mortality of any major cancer type. There's a limited number of predisposition factors that we know of and they're mostly lower penitence risk factors. The early warning symptoms and signs are relatively nonspecific. Pancreatic cancer spreads very early. It's very invasive and it tends to invade into both lymphatics and the Venus system very early on. That we actually can find it early with screening tests that we may improve, survival. This is a cancer where people lose a lot of weight. They can't eat or drink well. And actually that sometimes really causes us problems and it prevents us from being able to treat the disease as a aggressively as we would like. There are a whole host of drugs out there now that inhibit an oncogene called KRAS. Some of the tumors we've seen improvements in treatment and lower mortality has either been because of immunotherapy or because of new targeted drugs. AJCC stage is localized to the pancreas with no evidence of metastases. This is really the stage or stages one and 2 that we can cure in some instances. Most patients either present with larger tumors that haven't spread. A quarter of patients with pancreatic cancer are not known to be suffering from the disease. A sea change is needed in addition to new therapies moving things to earlier diagnosis. There are a number of families that don't know they have these mutations. Most of these are not actually found by surveillance. Suggesting that screening may be useful if you can find a high enough risk group that it is, appropriate. The study looked at mutations in jeans that predispose to breast cancer, ovarian cancer, and others. The first 6 were statistically significantly different than when they compared to a population database called Nomad. There's now screening recommendations by age and how to do this screening. People with familial risk of pancreatic cancer, either because of inherited mutations or also multiple first degree family members within the same family. One was an endoscopic ultrasound. An endoscope that requires an invasive procedure. Procedure requires some sedation. We also have been using MRI, which obviously does not require Sedation. This is a procedure where you use, magnetic resonance imaging together with what's called an MRCP just to pick up the Study looked at around 1,700 individuals. 26 pancreatic cancers were found. 3 quarters of the patients who were faithful to the screening program doing this every other year were found with early stage cancer. There were a set of individuals who sort of fell out of surveillance for whatever reason. It's actually not as you might suspect the easiest thing. To stay in surveillance when you have to do these types of procedures once a year. The 5 year survival rate among those who had prema ligna lesions was a hundred percent. The cure rate was much, much higher and patients did much much better than those here in the red line. There's very few patients we know of in the general population who have a risk like this and we'll come back to that idea. Because of this and a couple other studies, germline testing is now recommended. IPMS is an introductory papillary mucinous neoplasm. The most important thing about IPMS is they themselves are not invasive, right? They're not an invasive tumor that will spread to other areas of the body. However, they have the ability to transform to bec These lesions are related to about 10% of pancreatic cancers. Many people don't have them, but again, it is another place where we can start to find this disease earlier and try to treat it more effectively. The most strong risk factor for pancreatic cancer is age, right? This is tends to be an age of older adults, although that is changing as people have likely heard. GI cancers in particular seem to be rising in younger individuals. The median diagnosis is around the age of 70. It tends to be a higher rate in men in Ashkenazi Jewish individuals, which may have something to do in part with the familiar inheritance of BRCA mutations. There are a number of features related to systemic metabolism, how we process nutrients, weight, exercise that are risk factors for pancreatic cancer. Physical inactivity is a little less consistent, but seems probably to be related. Patients with pancreatic cancer tend to lose weight as they approach the time of their diagnosis. This is really a quite a unique feature of this kind of cancer. You don't s. n you would see in a circumstance like that. Diabetes over a decade or longer is clearly a risk factor for pancreatic cancer again with the relatives we talked about. Weight loss also actually causes hypoglycemia. The exact mechanism of this is not totally clear. People with pancreatic cancer start to develop hypoglycemia and the blood sugar rises. This is not something you tend to see in patients without the disease. About half a percent of people in the U.S. develop diabetes after they turn 50. Pancreatic cancer causes diabetes in addition to diabetes being a risk factor. We there are times that the cancer is there, but very hard to see. The pancreas is among the most difficult organs to image in the body. As the tumor is growing and the as it gets bigger, you're more likely to become hypoglycemic. It does seem to be correlated with the size of the tumor. Which then obviously it has implications for diagnosis. There's been a couple of very high profile papers, including one recently in Nature Medicine that did this. And so I think that when they're getting hyperglycemic, the cancer is there. I'm not sure always will be able to see it, but if you did serial inflammation in the pancreas in particular. This type of inflammatory insult is almost required in order to see the tumor develop. Smoking, heavy alcohol use, chronic pancreatitis are all risk factors for pancreatic cancer. In pancreatic cancer, we don't see mutational signatures of cigarette smoke. There's been this thought that this is an inflammatory insult, but there's not a lot of data yet to show that. People who drink a lot of alcohol do get pancreatitis. Chronic pancreatitis can happen from a number of different reasons. These all are related to an increased risk of pancreatic cancer. Pancreatitis can happen from blocking of the ducks that drain enzymes out of the pancreas into your small intestine. The tumor will sometimes impede the flow of the enzymatic fluid. Reverse causation in this disease related to a number of these risk factors is really important. And biologically, I think quite interesting too as we think how to leverage these things for early detection. The diabetes actually goes away. The tumor is actually causing dysfunction. Some of it's in the pancreas, some of it is actually peripherally that's causing the diabetes. There's almost like a parity of plastic syndrome. Cigarette smoking, alcohol, things that seem to be metabolically related like physical activity, obesity. The other big bucket then really is is inheritance, right? So either strong family history. Or inherited mutations. Most genetic mutations are between 5 and 12 fold risk, right? CDN, CDK and 2 A is. One of the genes that has the highest risk for pancreatic cancer, that actually is a gene that leads to familial melanoma syndrome. The studies I showed you where screening was effective, we think, although again, not randomized, but where we think we're able to catch some of these cancers early. Those patients we think had at least a tenfold risk of pancreatic cancer. Pancratic cancer is substantially less common than some of the other cancer types that cause a lot of mortality. There are certainly drawbacks to expanding the screening population. And we're trying to look at how we would do that in a safe way. In pancreatic cancer, we have a couple dozen that have been identified through a series of genome might association studies. These are actually worldwide studies. You really need studies from all over the world to do this. The relative risk for each minor allele or each risk allele is very low right so it may be 1.2 or 1.1 9. So any individual variant that you find is not going to allow us to screen, right, a particular group of individuals. What's now started to R 5 A 2 is actually a transcription factor that helps delineate self fate in the pancreas. There have been a number of really quite interesting studies that the gene dosage effect of NR 5 A2 actually changes the self fate within the Pancreas after an inflammatory insult. Pancreatic cancer is a rare disease. It's hard to get people to change their lifestyle because of pancreatic cancer. But as other public health interventions lead to healthier lifestyles, you would hope that we may also have an effect. There's a lot of work going on now in pancreatic exists, which is I think really interesting. We don't do this work in my own group, but I think it's quite cool. As we get more and more CTs and MRIs and things as a population, we will find more and The better we are at this, the more we can remove things that prevent people from getting pancreatic cancer in the first place, which would be an important thing. ere's been some really interesting studies using cell free DNA from the cyst fluid. Risk levels in the 8 to 10 fold range most likely to simulate what we're seeing in the familiar risk and when you sort of play out the numbers for positive predictive value that's about what we need. But maybe I'll stop for one sec and see if there's any questions or Comments. There has been also some concern that those drugs may actually lead to some inflammation in the pancreas and be a potential cause of pancreatic cancer. There's been a number of studies trying to look at this, which have been not definitive at all. The rate of pancreatic cancer has increased a lot in the past 10 to 20 years. Some of that has been thought to be due to obesity and diabetes. Do you think it would be worth it for people with melanoma to regularly be screened for this gene? CDC would need to decide what prevalence of the gene mutation would be among all of the melanoma carrier, you know, all the folks who develop Melanoma in the US. All of them so far as we discussed have really required that there be a family member with pancreatic cancer to do There's one more question in the chat. Maria, if you want to speak up, has there been any surveillance on how 4 month therapy use could either lessen or increase the development of melanoma. There's been a little bit of work on that. The next thing I wanted to talk a bit about was. There are actually features that the cancer will present. Sex specific differences and incidents and trying to understand why some of that may be is a very interesting question. If that happens enough in advance and you can aggregate some of these things together, it may allow you to actually pull people out of the population who should undergo surveillance. Idea over the past I'd say 5 Maybe 5 to 10 years, for a number of different reasons. Sir Ashtari has spent a long time, 20 years trying to think about an elucidate some of the relationships between diabetes and pancreatic cancer. And then we've done a series of studies ourselves together with Matt Vander Hyden's lab. There are a lot of changes happening in both before cancer is diagnosed and that this may provide a window for diagnosis. People often have abdominal discomfort from pancreatic cancer. That doesn't happen the day before they're diagnosed. Cancer has among the highest rate of Venus thromboembolic events like Venus, the leg being the most common. Changes in their food preferences, malabsorption, because one of the jobs of the pancreas is to make enzymes to absorb food. The medical record has become very structured in the medical record as medications. The dose is known the day it starts is known, the day gets refilled is known. So we decided we would do a proof of concept study using a couple of Harvard cohort studies. Study looked at how medication data can be collected every 2 years. Could this predict risk of pancreatic pancreatic cancer? The study was published in the Journal of Clinical Oncology. Starting of insulin was one, although any diabetes medicine actually predicted risk. Anticoagulants like we just talked about these patients are at risk for clots. Sometimes the clot actually precedes their diagnosis of cancer. In an unadjusted sense if they had a couple of these different changes upwards of 5 fold. And if you adjust for some of the other risk factors, we already know more like threefold. But this started to clue us in. AI algorithms can be used to segment all the organs in a CT scan. The yellow is the liver. The prediction is what the computer says is liver. And the ground truth is what a radiologist would have done. The study looked at the distribution of organs in the general population and then what happens in the time before someone is diagnosed with pancreatic cancer. It looked at skeletal muscle on the CT and also fat, so adipose tissue. It was based on some of the work we had done with Matt Researchers looked at CT scans from before diagnosis and patients with pancreatic cancer and match controls who do not get pancreatic Cancer. They found that as you get closer to the time of your cancer diagnosis, the amount of skeletal muscle goes down. The first paper doing this that we published was last year together with chisander who's at Dana Farber in Harvard medical school and Sauron Brun who's in Denmark. We started out somewhat simpler. This was a just using ICD codes from the medical record. There are now tens of thousands of different codes. You pick out again an individual who's at risk for the disease in the next year or 2 years. That relative risk is high enough that it justifies doing an MRI. weight loss can be seen in other cancer types, not just pancreatic cancer. Could you use this as a way to again pull people out of the population who should undergo some sort of cancer screening. There are some cancers that do this and many cancers that don't. When patients come to clinic to see their doctor, seeing that their weight has changed could be a signal that a cancer is coming in. obesity actually puts our body in a low rate inflammatory state. There's actually interactions between the epithelial cells, the acider cells that make the enzymes. Alpha beta cells in the pancreas. We used actually a number of different machine learning models. Which you can go to the paper to see this specifics. One of the advances of that paper was that it wasn't just the ICD codes you had. A study found that the new onset diabetes that happens from the cancer when it's paired with weight loss the risk of pancreatic cancer goes up dramatically. And so I think those types of studies will show you that it's the combination of factors that are happening. to one another. There are a number of symptoms that people get from this disease. These are things like weight loss, early satiety where people can't eat as much at one time. One of the things we've been studying a lot is how pancreatic enzyme secretion, which is what breaks down the food in your Signs means what the doctor can see, right, when they examine the patient. Once you can feel, say, a It's not usually a good sign. These are usually things that are a bit later in terms of the development of the cancer. The median survival is quite short, right? :39 So it's less than a year. There aren't that many effective therapies. Study particular cancers that you really learn how those cancers are treated and how patients experience those cancers. Trying to spend some time with an oncologist who treats the disease you're interested in is important. And even spending some time in clinic, I think is important because it really helped you understand the disease. His liver tests were somewhat off. Because of that, they then did a scan to try to figure out, well, what's going on with his liver. They did an abdominal scan and they actually saw a mass in the pancreas. There was not cancer and other organs. The patient had a small tumor on his pancreas. He had chemotherapy and surgery to shrink the tumor. The patient is now on the road to a full recovery and a new lease of life. The tumor is not easy to see. Machine learning algorithms are picking up that early on with early tumors, you see dilated pancreatic ducts, which is this dark stripe. And then after we gave 2 months of chemotherapy, you can see it's largely gone, right? The patient had no cancer for 3 years, but his tumor eventually did come back. He had to have surgery to remove it because it wasn't lung cancer, but pancreatic cancer. He was on chemotherapy for about a year, before he passed away. Third most common cause of death from cancer in the US. Early detection is a hard problem. But there are now, I think, a number of avenues that are moving forward to try to do this. genetic testing is now recommended for all patients with pancreatic cancer for the reasons we describe. We did a little less discussion about treatment, just given time. :32 But the patient I showed you is sort of a, an example of trying to use chemotherapy and radiation or chemotherapy and surgery Pancreatic cancer has been rising. It feels like it's popping up even more so in women than men, even though men still are at greater risk. Try those things with us that we make progress. Pancreatic cancer is also vulnerable to sort of this earlier onset that we're seeing for other GI cancers, but just if you talk a little bit about the genetic epidemiology. Some of the increase in younger individuals is more in women than in men. There does seem to be. when you have these risk factors, they do seem to matter more in younger individuals than older. That if you're obese or you smoke, that it increases the relative risk of cancer at younger ages. Obesity diabetes do matter more when you're younger. And then there may be other exposures we have that we don't know yet. find signatures in the tumor itself that tell you what's own was exposed to. People who have Just one first degree relative have a pretty modest increase in risk, a relative risk more around the 2 to 3 range. So right now, people have one first-degree relative are not being recommended for surveillance. Unless they have a genetic mutation. The exact cut point at which to say you should do surveillance is not that clear. We generally now will recommend people who have 2 or more. First degree relatives in the family with pancreatic cancer that all of the first degree relatives around them Get screened. There continues to be debate as I think you're alluding to. About whether we should be using family history alone. At this point we still do and those people still qualify for these. Both components, the individual and the group component are due on Tuesday, individual component, due at 1159 next Tuesday. The group component, regardless of which day you're presenting, the slides are due. Everyone is due at the same time. This should be doable in 2 pages single-spaced, but we do give you a little bit of wiggle room if you want up to an extra page. If you do it in less than 2. That's great. Heather Pi is the principal investigator nurses, one and 2. She's fine, but she won't be in class today. She did a nice interview of the Harvard Magazine, so I think we put an attachment on it. Graham Norton took a course on cancer prevention years ago. He's been doing this since he was 5 years old.

All right. Nice to see you all here today and looking forward to talking a little bit about breast cancer today. Feel free to jump in with questions. I'm going to ask you some questions as we go along, and I would love to hear your thoughts as we're proceeding with this. Go to this QR code We'll go through a little bit of descriptive and epidemiology, and then go through risk factors thinking about how risk factors or breast cancer occur across the life course. Think about reproductive factors. How endogenous hormones fits into this and underlies a lot of the risk factors Black and Hispanic women are more likely to be diagnosed with breast cancer than white women. White women have the highest incidence, rates of breast cancer. Black women haveThe highest mortality rates the fourth black and. Hispanic women have higher breast cancer mortality rates than whiteWomen. The rates of breast cancer do vary quite a lot across different countries. And so, any ideas about what might contribute to that. Why might we see this pattern more screening? That's an interesting point. So more sc Less developed countries die younger. reening might be detecting more cases of breast cancer. What else might differ obesity, obesity. patterns of risk factors could differ across the countries. Study looked at how rates of breast cancer change with immigration. Japanese immigrants in Hawaii and in San Francisco compared to whites in the U.S. It leads us to think that it's not genetics that genes don't change this quickly. Breast cancer ranks as the highest incidence cancer, in the in females, and it is ranked second in terms of the number of cancer deaths that it causes. The age incidence curve is quite steep in sort of early pre menopausal years, up to around the time of menopause. At younger ages black women have a higher incidence of breast cancer compared to white women. In terms of looking at Hispanic of any race you can see, the curve here tends to be lower than both. CNN's Dr. Sanjay Gupta looks at the breast cancer curves over time. He says we see an increase in the particularly in the 50 and older. And then what happens? Okay. There is now standard screening and mammography for recommended from the age of 50 or 40. In certain population and high-risk populations, even younger, with other mortalities, screening for about 50 years. The hormone replacement therapy that was found to be associated with that currently vascular races. So because practices were changed during that time. In postmenopausal women, and as they published their initial findings with an increased risk of cardiovascular disease. Breast cancer is a very heterogeneous disease. Different subtypes have very different outcomes in terms of prognosis. The prognosis for those, is actually a lot better now, because we have a targeted treatm. This is established based on gene expression. So estrogen receptor is one of the original classifiers of breast tumors. Those are er positive versus absent or er negative. Within those we can use a few other markers to help us define luminal a and luminal B. There are hormone receptor, positive tumors that are H negative or H 2 positive, and then her 2 overexpressing tumors. And then these triple negative tumors. So they're er negative Pr negative and her 2 negative. And I have the gray and pink. On the left side, this is looking at breast cancer, incidence and death. By race and ethnicity. So if we're going to look at a white, black and Hispanic as the as I had in the poll. If you compare these distributions between white and black women, what do we see? The light pink are the her 2 and hormone receptor positives. And then the Darpa Gray are the triple negatives. Negative tumors are harder to treat, and they're more aggressive. The proportion of tumors that are triple negative tend to be higher in younger women. There are lots of potential differences in structural access to care, treatment, screening. But there are also some molecular differences that are adding to that as well. There are structural differences in structural racism. acial disparities, but it shows up in a nuanced way in terms of the incidence and mortality that's good when you adjust for the subtype. One of the reasons is that they tend to have more breast cancers at younger ages. The higher incidence rate in black women in younger ages they're more likely to be triple negatives which could be contributing to this. There may be other differences contributing it as well. With breast cancer, there tend to be later recurrences, causing death. This is something that is a little more unique to breast cancer. With colon cancer, you're pretty much in the clear if you make it to 5 years. Most women who are diagnosed with breast cancer end up dying of another cause. But there is a significant breast cancer, death. at's something that is certainly a remaining question. To try to understand. Why is it that these tumors recur much later. 5 year survival rates for white women is 92% and 83% in black women. And we've looked already at the difference in molecular subtypes. And here you can look at the differences by whether the tumor is localized or has spread regionally or more distantly. Men do get breast cancer, but it is predominantly showing up in women. Some inherited mutations carry a very high risk of breast cancer over lifetime. There are also genes that are more common snps that contribute a little bit to increasing risk. There are risk factors that occur across the life course. We'll start with some of the earlier risk factors and think about how they could be impacting risk of breast cancer decades later, and what that might mean. This is a conceptual model that was put together from a working group looking at environmental factors and their impact on breast cancer. The rainbow is representing the fact that etiologic factors could come into play at multiple levels of thinking. Research shows that childhood and puberty are a particular window of susceptibility, for breast cancer. Women who were exposed in their 30s, 40s and 50s had not much of an elevation of risk of breast cancer compared to the women who were exposure when they were children. The radiation causing mutations that can then be carried on. They're impacting much more in the younger women. This really highlights for us that something really important is going on in the breast issue at that time. In premier puzzle women. e women to tell us what their body shape was like at age 5 and age 10. And then at age 20, and we can think about an average of 10 and 20 as being what they were like adolescents. And what we see is the following. What a woman's body size was in in adolescence is impacting risk of breast cancer in her. In postmenopausal women. There's something going on at that moment that is potentially a set point. Japanese population, African, American, Scandinavian, all show this lower risk of breast cancer with higher weight at adolescence, child or adolescents. So it's really quite consistent over many, many studies question ready for biological explanation. Age at monarchy is a pretty well established risk factor for breast cancer. This shows decreasing risk with every year later that monarchy occurs. If overweight, girls are more likely to have an earlier period or a later period. The earlier monarchy starts the earlier you start on this you know, big curve of being exposed to estrogen estradial over the life course. Bmi is associated with higher odds of having an early monarchy. overweight is usually associated with an earlier monarchy. Over time, age at monarchy has been getting earlier and earlier. It's gone from an average age of 1716 to, you know, down 1211. So we can then think about how things like this could impact risk of breast cancer. There are some shifts in our diet and lifestyle habits that are contributing to some of those shifts in monarchy. There are probably other avenues and pathways that that are could be explored in terms of trying to understand that. Pregnancy and age at first birth can reduce the risk of breast cancer. It doesn't increase the risk, however, of eating grants and system childhood adiposity. It is not a risk factor for other cancers. Women who have more pregnancies have a lower risk of breast cancer. If you have a a child late in life, then that we call sort of the bump of increased risk after pregnancy never quite comes back down. Pregnancy throws all these hormones at the breast tissue, and can contribute to replicating some of those mutations. Women who have a childbirth much earlier, that window between monarchy and childbirth is shorter, and fewer mutations would have had the chance to accumulate. Pregnancy and birth is sort of a tricky one in terms of thinking about the impact on breast cancer risk. Typically, we think about this window of susceptibility after a pregnancy as being sort of between 5 and 10 years. There's been evidence that that suggests that this benefit is particularly notable in triple negative breast cancer. And again, those are more likely to be diagnosed after pregnancy. So, having this benefit of breastfeeding on the breast tumors, particularly the triple negatives, it's a The later an age at menopause is, the more it stretches out that exposure to high levels of Estradiol. A woman who has a bilateral efrectomy. before the age of 45, has about half of the risk of a woman who goes through menop.ause after Early puberty at age 11 or age 15, for natural menopause, it's usually between 45, and 55. But you see that early days :03 so early monarchy is not associated with earlyMenopause. It's just a question of you can have variation in both spectrum. infertility treatment, does that impact breast cancer risk? And there's been a lot of studies on this. Nothing is showing up as being either terribly consistent or terribly strong in terms of it being a risk factor. Pregnancy makes a difference because of what has been probably accumulated in breast issue up to age 35. After a late pregnancy that you end up with as actually being at a higher risk than Malibu. The birth index is a way of accounting for the age of pregnancies, the number and the spacing between the births. pacing of the birth. Hormones are acting as growth factors, and this increases opportunity for replicating a mutation. There's also the possibility that estrogens could be contributing to cancer through genotoxic mechanisms. So estrogens get metabolized through hydroxylation. that already exists in the tissue. Estradiol in pre-menopausal women is hard to look at. tic rate, the rate of division of these cells in the breast. Epithelium is higher at that point. So this was a good hypothesis. Women who tend to be on the higher range of normal for circulating estrogens have a higher risk of breast cancer. And then, in looking at Android, so circulating testosterone Andrine Dione, it is also fairly consistent across studies that higher levels in premenopausal women are circulating estrogen levels which are much lower than they were in premenopausal women are are related to how much adipose tissue there is. Women who are in the top 20 to 40% of those circulating levels are at a higher risk of breast cancer. circulating hormone levels were still predictive of risk. If somebody had a higher risk of breast cancer based on their pregnancy, history, and their family history. And we see that it's similarly predictive of higher risk, independent of some of these other risk factors. Adiposity throughout the reproductive years is associated with a lower risk of breast cancer, too. As a woman enters menopause, the adipose tissue that she's carrying is contributing to those circulating hormones. This is one of those hard to think about in terms of public health messaging. But this is very, very consistent. This is a more recent pooled analysis that pulls together many, many studies, including our health study and nurses. Women who gain weight have a higher risk of breast cancer after menopause. This is among non-hormone therapy users, because again, we know that adiposity contributes to circulating estrogen levels. Women who lose weight after menopause are at a lower risk of breast cancer. Adiposity is contributing to risk likely through a hormonal pathway. Women who have lost weight and were able to keep it off are also at lower risk. Your adipose tissue and those circulating estradiol levels. It doesn't matter whether it's intentional or not intentional. It is contributing to lower estrogen levels overall. M to matter why women lost weight, so you can think about was the weight, loss, intentional or non There are a lot of differences between the randomized trial and observational studies. Once women go off hormones, as we saw in that decline in the incidence of breast cancer over time, they have a lower risk. This is sort of a nice figure looking at the incidence of breast cancer. Among this is across Bmi, so different categories of Bmi and looking at estrogen and progestin use so exogenous hormone therapy. So this sees a a difference, but still an increased risk. Oral contraceptives are associated with an increased risk of breast cancer. But oral contraceptives tend to be taken by younger women who are at lower, a lower risk of developing the disease. If it's brca, one or 20, great question. Alcohol is a very consistent modest but consistent risk factor for breast cancer. Carotenoids are the colorful fruits and vegetables that are high in Alpha Keratin and Beta Carotene we can see a lower risk of breast cancer among women who have higher circulating levels of carotoid. Carotenoids are more beneficial for preventing these more aggressive, harder to treat tumors. Physical activity, modest but pretty consistent, associated with a lower risk of breast cancer. Menopause had a lower risk of breast cancer compared to women who were consistently low physical activity. adiposity, menopausal, hormone, therapy, alcohol, physical activity and breastfeeding. Dense breasts are much harder to find a tumor in compared to fatty breast tissue. It could be that the breast density is a masking the tumor, and that it's hard to detect. 10 years later women who, with dense breasts have a higher risk of breast canc. There's still some that are gonna be hard to detect. We see a mammographic density associated with both er negative and er positive. The women who were more overweight as children :21 have lower mammographicdensity much later in life. The association between childhood adiposity and breast cancer risk is mediated somewhat by mammographic density. So it's like between 30 and 50% whether it's Premenopausal or postmenopausal women. Biologically, we're not understanding it yet. Can you name a breast cancer risk factor that was new to you today? :16 And I'll switch over to the final question here. :25 Are there anything that you had not heard about :31 adipasty. We're going to turn it over to Colleen Michelle, who are going to give a presentation about survival in cancer. And then, after that, we're gonna discuss the article that was by welcoming day. We'll actually have you turn to your neighbors and have a little group discussion 6% of people said, prostate cancer. 18% said death from other cancers. 12% said Alzheimer's. But in fact, the main cause of death is cardiovascular disease. And if you looked at currently today, all prostate cancer patients, about 30% of deaths, cohort is cardiovascular You are hosting an office hour related to the letter to the editor this afternoon, right after class. If you have any questions that is due on Thursday at midnight. You are welcome to work on your own or up through groups of 3. The team will be meeting on Thursday to discuss cancer survival and survivorship. You should have gotten your presentation assignments as well. The text of the letter yeah. The header could be separate. We'll provide an overview of the burden of burden of cancer survivorship in the Us. Discuss a proposed research framework for working with studies of cancersurvorship. Michelle will talk about some next steps in this research space. Current estimates are that there are over 18 million individuals in the Us. Who are considered cancer survivors. It's projected that this group will increase as well with an estimate of over 22 million by the year 2,032. The older age groups are where we see the greatest proportion of individuals who are considered cancer survivors. This can be attributed to a number of different things, including screening and diagnosis and potential over diagnosis as well as treatment advances. 2 thirds of cancer survivors are over the age of 65 in the Us. uals at earlier stages as well as treatment advances where hopefully able to extend the survivorship period within reasonable burden. The majority of cancer survivors in the Us. Are breast cancer, prostate melanoma and polar rectal cancers. Stage is another really important factor to consider individuals. In the Us. just over 600,000 individuals are metastatic cancer survivors specifically, and this figure itself has also projected to increase. who are diagnosed in their earlier stages might have better treatment options potentially curative treatment options. The cancer survivorship care quality framework was created. It is an interplay of individual interpersonal organizational community and policy factors. So this framework serves as a foundation to define 5 domains of cancer Survivorship care as well as general needs. Cancer survivors are at an increased risk for reoccurrences and new cancers. Hormone receptor, positive breast cancer endocrin therapies used as a adjuvant treatment to reduce the risk of reoccurrence. Cancer survivors are at risk for physical effects of cancer as well as treatment. Side effects include nausea, fatigue, constipation, diarrhea, hair loss, chemo induced neuropathy. Psychological effects include anxiety, depression, cognitive changes, fear of reoccurrence. Social effects include financial toxicity, loss of work, productivity, return to school change in insurance status. Physical effects and psychosocial effects after treatment are some of the domains that we want to focus on. There are some high prevalences of front conditions both before and after diagnosis of cancer. Non-related non cancer-related conditions include hypertension diabetes, cardiovascular Cancer care for cancer survivors is complex in the Us. n. We have a very complex health system. Measures can help researchers identify gaps in care. The Tcg. 30 is a validated questionnaire for health, related quality of life among cancer survivors. It is applicable in over 100 languages, which is a functional assessment of cancer therapy questionnaire. All cause mortality, where we're looking at the total number of deaths across the population. We're concerned with death due to a specific cause, say cardiovascular disease. Relative survival, which is a comparison of the overall survival for a specific cancer site. Among the total population of patients, there are a number of potential biases that we think about often when we're designing studies of cancer survival. These are not unique to cancer, epemiology, or even chronic disease equity, but we do see them in this space fairly often. Mortal time bias can be defined as a period of time where it's not possible for study participants to have the event of interest, such as a death, for example. To handle this, there are a number of different modeling frameworks and decision to make as someone who's This is a really complex issue, and if you want to learn more about it. You can take bias at B 203, where you'll have a great Tf. Next semester. We'll talk about this Michelle. The ideal way to make sure that you don't have a mortal time bias. One of the ideal ways is to emulate a target trial. You could also take that period of time where your treated individual is not being exposed at that point in time. N. n which a cancer is detected by screening versus the time. between which it would have been detected by symptomatic presentation and. going to the doctor and diagnosed. If we attribute that the null hypothesis is true that screening truly doesn't have an effect on prolonging someone's survival More indolent tumors have a longer screen detectable period than aggressive tumors. And again, this can overestimate the effectiveness of screening. And the last issue we wanted to raise was on prevalent users. Next steps in cancer, survivorship and survivorship research. We can use research to improve clinical care, quality of life and understanding of adverse effects of treatment. We can do this by defining population needs for various cancer sites. There are a ton of different ways that we can measure a health related quality of life for cancer survivors, including the Ertc. Having a standardized method that is commonly used, can allow us to compare more studies that are looking at the same outcome being The Nci office of cancer survivorship actually posted this on their twitter yesterday. And we wanted to share this graphic where it shows the number of cancer Survivorship brands that have been funded by the Nci. As of 27 since 2,017. The research we conduct can impact the community level to the Federal level, not to mention policies that impact insurance, professional organizations that promote cancer care. And lastly, we can think about how we can implement full cancer survivor care quality framework in We're always happy to talk about it. We both asked our Pq. 2 very recently, so we're happy to chat about it whenever. I wonder if you could. Just I think that examples of lead time bias in particular, and as well as the other biases, are interesting. Think of like metastatic disease, like someone who's like there's no potential like next steps like in a very extreme case. So maybe they decided to get strained for some reason, before symptoms appeared. But the disease had already progressed, and then comparison to someone CNN's John Sutter has put together a slide deck to help people understand the findings of a recent article. Sutter: Why did Welch and Day even write this article? What was their motivation? And are there things that you wouldn't know about? We'll come together, maybe at 30'clock for for discussion. But really talk about whatever you wanna talk about anything that really resonated with you anything that gave you a little bit of pause and talk with your your neighbor. Is it actually hurting people to be undergoing this process? :42 Right? So right? So some people may get safe. But they're you know, downsides, like :57 some people can. Can even die from unnecessary surgery. Cancer is only a percentage of total deaths. You actually, even for pretty common cancers, seems kind of small. So an easy way to think of it is, I think Colon, cancer is a common cancer. Spend a lot of time studying it. CNN's John Sutter asks the Colonel if he thinks screening is actually more important than he's making out on this. Sutter: "It wasn't clear to me if panels C and D are real data" There's no methods also. So it's hard to say exactly where they got these data from. They just said, We expect, based on the outdate of these trials and 30 years of follow up that 70% of the population to be dead based on basic demographics. The first publication of the trial showed a benefit from screening on prostate cancer. The total numbers of deaths were almost identical in the screening and control arms. But that's out of 1,730. That's at least chance. The number is going to be too small for the total number. So so that's the main point, I think. Why. uccessful. But :04 like so for colorectal, they estimated. Was it like 5.9 million? Leonard: Most patients with prostate cancer would not die of prostate cancer. Most of the patients with leukaemia would die with leukemia perspective. I've shown :00 next step for a brief way to evaluate that. The difference of dying cancer is really really small compared to :40 countless of other reasons, whether it's like a disease or even an accident, because you have all class mortality. So also, that's why you would need such a big number of patients with cancer to actually test that. Cancer is just like a small percentage. So you're gonna like, reduce your effect size in comparison to the population. And then you need more patients. Make the argument that you're not saving lives anymore. The whole point was to save lives that were like from :20 the cancer, and not just more generally. I feel like it's a big ask of a patient to accept this uncertainty. High-risk groups would be especially stressful. I was wondering, this doesn't seem like it's going to harm people. So why are they so focused on mortality? I don't see how that could hurt you. Mortality is really a measurement that we look at. Multi-cancer detection assays. Many of them don't even aren't specific to it's elevated. They are expensive, even though they're not expensive on an individual assay. If you have millions and millions of people :07 pretty substantial, false positives, false negatives. I think that this measure would actually cost more expenditure on the long run. Cancer is not the biggest death based on their beta. So maybe we should be allocating most of the money to all of the releases. The US Preventive Service Task Force came out strongly against prostate cancer screening in around 2,012 and then updated it to a more. sky procedures. They quoted 40% :14 mortality after surgery is not cancer-related, but it tends to be riskier with higher Screening itself can cause stress, unnecessary stress to the that person's life. It's better not to know or to just wait till the cancer is very advanced and you're diagnosed. I think age is another :01 important aspect. Like prostate and colorectal. I'm not sure about breast. There's a cut point where you usually don't recommend doing screening for prostate Psa. A lot of these statistics are population based. We're talking first and years. But if you look at it from an individual perspective, it can be quite different. 2 out of 10 people will die 10 years prematurely. I was struggling with the same thing. I should start looking at like how that's determined that something would not eventually go on to cost mortality. That's kind of another similar as individual versus population. You can't tell on an individual basis. T. t. It's like Laura, like talked about, you know, pseudo cancers. That's basically what that means is, histologically, they look like a cancer. Do you think that early detection for most people can extend the number of volume life years? Is it just like all of that time, you can detect it so early. You're going to be undergoing treatment, and that's decreasing quality of life, or all of those remaining 10 years. Probably I mean, it's a great question. It probably depends on answer. Conrad is a physician, scientist trained in internal medicine, received his mph here at the Harvard School of Public Health, and has been engaged in really very innovative research across the pathogenesis and cancer continuum and prostate cancer. He's an assistant professor, both at Harvard Medical School and Lorelei, welcome everyone. I'd love to talk with you today about 3 fundamental things of prostate cancer. The first one is risk factors and primary prevention. The second part is around screening Psa screening. And then the last part will briefly talk about cancer, surviv The prostate is probably the most boring organ in the human body. It's hidden in the pelvis. Half of humanity can very well, and maybe even better, do without it. The prostate is cancer. The prostate is a common place for cancer to originate. There are 2 dimensions that are important when we talk about it. One is how big is the cancer and how much is there? And we'll also talk about grade. There are basically 2 common clinical presentations of prostate cancer, or 3. The first and most common one is no symptoms at all, and the cancer is detected by Psa screening. The second one is, you can imagine this tumor growing and pressing on the Urethbrasine The majority of cases, at least in the United States nowadays, are of T stage onec. Not metastatic, that are detected by Psd Springs, so by blood tests only, and are not even culpable on the organ. relative survival is a comparison to people typically of the same age and in sex, or what the cancer registry or courts over the 5 years. So it really depends on who is diagnosed with cancer. Survival of people with localized prostate cancer is very, very high, but it is still bad for people with metastatic prostate cancer. Cancer is a big public health burden, and we'll talk about these are cancers, localized prostate cancers. There is no curative therapy for metast An AI algorithm that looks at the tissue and then picks up what is bad about it. This patterning was actually created by a pathologist, looking at many cases and sort of deciding visually. Laura Stepp: What do you make out of these numbers that I'm showing you here? She says they show the prevalence of prostate cancer at autopsy of men who died from other reasons than prostate cancer. Stepp says the scale goes from 0 to 60%. The prevalence of toxic cancer at autopsy already goes up to very high levels for 30 to 39 year olds. African-americans tend to have a larger percentage of prostate cancer. That's why they are having diagnosis. Life expectancy is a lot shorter in black men in the United States. There were just fewer studies also. So the data weren't sufficient to come up with reasonably precise esti. This is a, this is actually a meta-analysis. This isn't just one single original study that I pick because it is really a pooling of autopsy studies that were available up until, like 10 years ago. The left side of this slide shows you what we could find if There is way, more plastic cancer that could be diagnosed than what we are, even currently with very intensive screening diagnosed. So let's focus a little bit more on how prostate cancer looks like in living people, because at the end of the day that's a little more important Prostate cancer incidence and mortality don't for one, differ dramatically between different regions, and that they, as you can see don't track very well with each other. Why, why, that might be, we'll be seeing. When Psea screening came around in the early. re is, we see a jump in the incidence. So in the number of diagnosed cases every year in both racial groups, slightly differently. The Psa test is actually not a bad test, but it's not been used very smart US Preventative services task force recommended against prostate cancer screening. In 2015, they changed course and recommended prostate cancer screenings again. So then, you see incidents going up again. There's the stark difference between the black and the curve for black and for for white men here for the United States. And we're we're more notable in in the in the back group. That's apparent. There are huge changes up to 5 fold in the same country of prostate cancer mortality rates. And we see such changes for other cancers, too, not always in the the same direction, with the same patterns. Medical care changes our ability to even diagnose it. Prostate cancer is a cause of death. We're splitting up the same disease into more and more categories. So it's always a problem in these long-term comparisons. In the United States, when people die here, what percentage of people get an autopsy? Or let's say, how many don't about 97%. Actually. So it's something that we don't do any longer. The autopsy rates were a lot higher back then. Of those 199 people, 178 were found to have died of cancer on their autopsy. So actually a pretty high, positive, predicted value. considering like this is why do I look on they didn't have computer tomography. There were 30 people here who were said to have diagnosed have died of heart attacks on near embolisms and so forth. They actually died of cancer based on the autopsy. So the sensitivity of the death certificate wasn't perfect. So there was actually more cancer. In order to have a good answer for you, I think we would actually need this type of study? Yep, yeah. And vice versa in a country that might be lower resourced. And so how good is it there having that comparison. The death certificate may not reflect the entirety of what we know about them medically, even in life. This was Eastern Germany before the reunification services behind the Iron Curtain. There wasn't a lot of technology, it was medical training, but there were no American textbooks. The underlying cause of death is actually cancer. That's what people ultimately die of, but that is the immediate cause. The argument is, people would not have had this this black client had they not had the cancer. 300,000 people are expected to be diagnosed with prostate cancer in the United States this year. 35,000 deaths are expected this year, which is about one in 9 of every death from cancer. There are 3.6 million people in the Us right now. The mortality rate in black men was 2.1 fold greater than in white men. If Asian were and Pacific Islanders in one group were the reference category. Then we're talking about a fourfold difference. And they're only in gastric cancer. Eric Zuckerman: Inherited genetics are not the only cause of cancer. He says lifestyle factors can also play a role. Zuckermans: Migrants are a generation l. White Hawaiians have a substantially higher risk within a generation than white Hawaiians. Even within 2 generations, for both breast or prostate cancer, the levels of risk don't reach that of the other archbishop. Men who have a brother or a father who has a diagnosis of prostate cancer have a 2 to 4 fold higher risk of the disease themselves. Men with a mother or sister with breast cancer also have a 1.5 to 1 point sevenfold higher risk. There's a lot of variation between our own genomes. At millions of sites in our in our genome for cancer risk, there are 2 things that are that are relevant. One is these rare but highly Pentrans mutations. Those probably explain about 5 to 10% of cancer. These are genetic epidemiology studies. They're small individually, but when we sum them up over the entire genome. We can create scores that at the end of the day are actually quite useful for risk stratification, as I'll show you in a second. There are 451 variants, single nucleotide polymorphisms or snps for prostate cancer risk that are statistically highly significant. Some of them with a P value of 10 to the minus 600. The effects of each variant are very small. Polygenic risk scores are very, very strong predictors, and they will probably be used clinically within the next few years, increasingly more, not just for prostate cancer. Prostate cancer is is one of those examples where they perform the best. There are many common conditions wher polygenic risk The percent of men who seem to have prostate cancer save in that age 40 16. About 30%. And so if you look at even at the group that had the highest polygenic score, the greatest genetic risk. What was

The majority of what could be diagnosed is not being diagnosed. Even this year is a very highly screened population. 80% of them actually got Psa tests. Not an insignificant percent of those cases were bad policing scores. With the data that they had a few years ago the Aeoc didn't get better anymore. Once they added, more snps into the model. But it doesn't mean that these things don't cause prostate cancer any longer. Non-genetic factors could explain up to 43% of prostate cancer risk. 25% of you said that genome, wide association studies of common genetic appearance will ultimately explain likely less than 57 genoc. factors. There is common genetic variation, and then there is rare genetic variation. There are things like Rocket, one, Brachit, 2, and so forth. 10% of cancers are probably caused by them. This is the one where it tricked you with a with a confidence. :04 But this goes back to the 1,900 thirtys to :07 big debate in :14. The camp of the Eugenesis, who thought that humanity could be improved by basically killing people. So the genes and the environment don't sum up to 100%. :09 So I fooled you by giving you, even though comfortable, with the same development that it seemed like you could subtract one from 100% and get the same. ironment. A genetic factor is too. esponsible for 100%. And we can even act on these. We could maybe eliminate cosmic radiation, which is nonsense. And this is something that is being clinically done, we may have better interventions. We have more shots at cancer prevention. Germline variants increase the risk of prostate cancer, but non genetic factors increase particularly therisk of aggressive prostate cancer. And then there are issues around treatment, access per and all of these things are relevant. We've seen that cancer initiation is something that comes very early in life. We've seen among year olds that there is a lot of prostate cancer already. So we want to prevent that from happening. height is :16 a strong risk factor for prostate cancer. And actually, other cancers, too. height is actually interesting with regards to that life course that I just showed you. Because when do people get taught? While during puberty. In cancer epidemiology, there's often a long time between when somebody is exposed and when we see the effect of an exposure. If we did that, if we threw them all into one bucket, age, race, and family history would come. Being pregnant more often decreases the risk of basically hormone receptor, positive breast cancers. Obesity is a very strong risk factor for kidney cancer from Demetrius cancer. The list of risk factors that people can universally agree on is shorter than for other cancers. Those are prostate cancers that are no longer confined to the prostate cancer that people die from. And all of a sudden that list gets a lot longer, because if you keep searching for risk factors for total plastic cancer, those are cancers. There's no information about subtypes on the medical record right now. The gene fusion between 2 genes er g and tempus 2 :17 is about present in what half of all prostate cancer. There is at least the suggestion of a protective association among erg positive prostate cancer. The results are even stronger among men who were all undergoing Psp screening. More physical activity goes along with more Psa tests so leading to diagnosis of cancer that otherwise would have not been diagnosed. The causal effect of :55 maybe preventing prostate cancer could be masked by that. genetics and environment are not mutually exclusive. But what about people who have bad genetics meaning. there are higher risk because of genetics. Is there cancer risk still amenable to prevention? There's very little prostate cancer among people with low genetic risk. People with a healthy lifestyle have substantially delayed an onset of metastatic and fatal plastic cancer at much lower rates and lower lifetime rates. People at a high genetic risk are just as amenable to screening as people with low genetic risk. But in absolute terms, as you can clearly see from these primitive incidents, curves, their benefit is even much higher. Psa was meant to be a marker just for measuring progression of prostate cancer, but was quickly repurposed for screening, for prostate cancer. When it reaches a certain level, then it typically triggers a biopsy of the prostate. There's been a lot of talk about whether prostate cancer screening works, and particularly in the United States. The American trial showed that it didn't work. But it turned out over the years that actually the American trial had not worked. This is how mammography screening looks like, too. This is how many people do you need to invite. And this is then the number of people who need to be treated in order to prevent one death. Screening does detect more cancer. When we looked at the trends over time, that hump in prostate cancer incidence. That's exactly the effect of of what it does. It's not a colonoscopy where you move a precursor. Task force has been going back and forth about whether screening is recommended. And that's why you see these changes in incidents over time. And of course there are concerns about when you don't screen. Prostate cancer is a major public health burden with strong racial disparities both for incidence and mortality. Puberty is a critical period for exposures that affect prostate cancer. This is a cancer that really still needs a lot of work. The risk factors are really for advanced prostate cancer, the ones on this one pattern that we've seen insulin and growth factors. Factors during the life course have a big impact. And we talked about Psea screening. It reduces on prostate cancer mortality.