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. We'll give you about maybe 25 s to think about it. The winner is response, history over here. If anybody wants more time, just raise your hand. We're going to call it. and and you just hit escape to see the answers alright. Yeah, got it? Oh, interesting. So what you'll learn about breast cancer when Dr. Eliason gives the lecture is that excess body weight early in life? Well, that is. that's true. The Harvard Crimson is a weekly, offbeat look at what's coming up for students. This week, the Harvard Crimson takes a look at the students' upcoming assignments. Students are asked to share their answers to a series of questions about their work. The Harvard Crimson will publish the answers in a weekly Newsquiz, and the answers will be posted online. Harvard will be using the all of Us research program to look at the association between air quality and cancer risk. How do you approach reviewing a a paper for a journal article? Usually you wanna look through and think about the study design. And so that the results? And and have they interpreted the results like correctly, or have they? The one of the bigger assignments is the cancer epidemiology pro projects. There's gonna be an individual. Write up on the descriptive epidemiology of that cancer. And then, you're gonna have a group presentation where you present on the association between a risk factor and cancer. Starting at 50'clock today, so start thinking about which of these cancer sites you'd like to take part in. There is a cap. So if you're really excited about a certain cancer definitely, try to log on as soon as you can at 50'clock. So you can get in on that cancer. Honestly, each of the cancers that is listed here is really fascinating from an epidemiology perspective. Family history can be used as part of an epidemiology study. You could send out a questionnaire to. a case control study or cohort and just ask people, and how, what kind of questions would you want to ask? So how do we? How, when you think about family history. of in doing an Epidemiology study? In terms of shared exposures within the family kind of,Yeah, yeah, absolutely. Do you think about if you were putting it on the questionnaire? Sorry I want to put you on the spot. But yeah, any thoughts about how you might ask some questions. Maybe specifically about family history. How might you ask the question? You really might be thinking about primary like first degree relatives. And then, you know, with with the advent of of genetic testing, or even things like 23 me, it might be interesting to know, did you have any of that testing done, and could we get those results back? Even your parents might at that point might not be old enough to really be at the highest incidence of cancer. So 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. In certain populations, understanding family history is much, more, much more challenging. And then, in terms of the recall bias. go back to your point. If it's a case control study. And so you're asking people who have cancer who don't have cancer. And you may think about it differently. Sweden was able to go from the time the cancer registry first started in Sweden, which was in the 1950 s. And then track multiple generations so they could link the birth registers. So they knew who was related to whom in the register, and then they were able to tag on the how those people had cancer or not. When you're looking at the relative risk estimates and 95% confidence intervals for risk of breast cancer with family history. So it looks like the the, you know. There's a stronger association. If you have 2 sisters, a mother, sister, and even a stronger with mother and brother. One interesting epidemiologic approach? That people have taken is, instead of studying family members to really, specifically look at twins. So if you you think there's 2 main types of twins, others, these on identical or monozygotic twins who share in theory 100% of their inherited genome. Swedish twins share 50% of their genetic factors. The fraternal twins or the dizygotic twins twins share more genetic factors than the monozygotic twins. If you're an identical twin versus if you're a fraternal twin, you can almost take away the environmental component by subtracting out the effect. In the 1950s, researchers in Scandinavia 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 Y axis. 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, you can sort of see, there seems to be both a genetic and shared environment component that leads to the overall risk of cancer. Genetic factors have a small role, but much more so environmental and lifestyle factors play a role and colorectal cancer. And then melanoma seem to have these very strong genetic factors. It doesn't mean it's only genes. It could be genes interacting with the environment, but they both have a strong genetic predisposition. 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. Another example is in bladder cancer, where there's certain genes that modify. Your ability to metabolize alcohol. Most genetic variants have very, very small effects on diseases. Rare variants cause disease in a Mendelian fashion, meaning, if you have the gene, you're gonna get the disease. Huntington's is a prime example of that, that. If there's that sort of Mendelians, maybe some of the cancer syndromes get close, but they're much more in this middle phase. 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. But for these families that have these germline mutations, they're pretty awful. The risk of certain cancers occurring is very, very high, and it gets passed from generation to generation. There's there can be many cases in a family with the same type of cancer, especially if it's uncommon or a rare type. Other features of hereditary cancer syndromes are cancers occurring in the sex not usually affected. Lifer-mini syndrome was really identified by Doctors Lien formini back in 1,969. Brca, one and Brca 2, and breast cancer and ovarian cancer are probably pretty well known to you. Interestingly, they seem to be playing a role in other cancers as well. The Gene, p. 53 plays a broad role in cell growth in cell cycle arrest in DNA repair-related mechanisms. It can play a role in apoptosis which is basically programmed cell death, and it can eliminate any damage cells. So it plays a really important role in cellular growth as well as making sure it gets rid of any bad. P. 53 is one of the most commonly mutated genes in in tumors across an array of cancers. If you get one bad allele with a p. 53 mutation, all you need is one more in order for cancer to be occurring. So so you're already kind of more than halfway there in getting cancer. The mortality from cancer in humans to that of elephants is between, say, 10 and 25% in elephants in 4.8 in terms of average lifespan. It's pretty similar body weight much much higher. So there's more cells. and so unfortunately, while you can't probably prevention, for these families may be hard. The number of cells is is exponentially higher. While humans have 2 copies, alleles of elephants actually have 40. So they all are slightly have slight modifications in the proteins they produce, but there's so much redundancy in this pathway, so, instead of having to knock out 2 alleles in elephant, you'd have to knocked out 40, actually. The risk of colon cancer in the general population is about, say, 5 in a family with lynch syndrome. 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. A lot of what we know now about what causes cancer in terms of inherited genetics has come from doing genome-wide association studies. And so, and then, because you're looking at millions of single nucleotide polymorphisms. Usually you set your P value fairly, conservatively at 10 to the minus 8 here. This is actually a Manhattan plot from prostate cancer. The individual effect of these variants, though, is really small. So the relative risk, if you have this variant versus. this variant, is just a P. Value. But these are the variants that seem to be kind of potentially interesting. Over 450 genetic variants have been identified. What if you took all of the variants together and created some sort of score? And that's what we do with apologetic risk score. So you're basically like, right, here's variant one. Do you have it? Yes or no. plus variant 2, yes or no, and maybe you weight it by the strength of the variant. You can look at people who have the highest genetic risk, because maybe they have. 100 of the 400 variants. And you can really start to see big differences in risk prediction. And so this, I guess, is just to say, you know, in terms of the these Gwoss studies have really helped to. There are on this plot, 450 unique genetic variants, with a P. Value greater than 10 to the minus eighth. that are associated with prostate cancer. And then you make a simple score, and you take each variant. and for each person say, Do you have it or not? Polygenic risk scores are a way of looking at the absolute risk of cancer over someone's lifetime. 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? That's the question for cancer. but we aren't using them clinically. The Ji-wa snips, I would say in general, I haven't been translated yet. Now that's different than say for lynch syndrome. where, if you are a family member and who's part of a family that's known to have Lynn syndrome? Then you are, Gonna use that genetic information. And for a range of of potentially different cancers. So mortality and fatality, what's the difference? What's mortality rate? Yep. And again, with time? Exactly right? So it's very similar to incidents, because the it's the number of cancer deaths. and then denominator instead, divided by the population and then over time. The mortality rate for some cancers looks much lower than for other cancers. But really, when you look at the vitality, so what happens in people who have the cancer, it can look pretty pretty awful. Can you think of a a cancer when the cancer has a very low incidence rate, but a high fatality? It's really a population level statistic versus the fatality which is really telling you, what's the prognosis in people who have cancer. So if you have a highly fatal cancer, the prevalence may look kind of low because the duration someone's living with that cancer is is very short. So basically, this is a simplified formula, incidence, times duration. Dali: Have you ever heard of the concept of years of life lost? Yeah. Here's a life lost that's close. That's that's Dali's or disability adjusted life here. Dali: If your incidence is high, but your duration is low, your prevalence is gonna end up being pretty low. 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. So that's why I'm saying I don't know if they changed it. 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 the blue the lower the rate. So are there populations that seem like there are greater risk for this cancer? Yup. it can help visualize disparities. Average life expectancy in parts of Africa might be 15 or 20 years lower than say in North America. We're independent of the fact that there's a different age of distribution. So if you wanna make these kind of comparisons, sometimes you wanna take away the effective age, and to do that, you can do age standardization. Cancer incidence rate per 100,000 people is based on the number of cancer deaths in different age groups and for a specific year. So basically, like. now, 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. A group in upstate New York wanted to look at prostate cancer mortality rates to see if there were racial disparities. So they had the number of cancer specific deaths in white men and black men. And then they calculated the prostate cancer deaths per 100,000 people per year. In white men, the mortality rate was 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. So the question that we're trying to answer is. are there racial differences in prostate cancer mortality that are not due to age? Right now, on average, the black men in the whole population are younger than the white men. We see that is separate from any difference that there might be from age. So what what were your thoughts qualitatively on, on what might happen if you did an age adjustment or age standardization? 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? And you're going to downweight in the white men. So ultimately, there are racial differences in mortality from prostate cancer from this population. Case control studies are often done in cancer, particularly when cancers are rare right? Because even if you had a cohort of 100,000 individuals for some cancers like glioma, or maybe childhood cancers or cancers that are fairly rare. So that would be sort of the cohort. And even, you know here I've just made it very simple that you're either exposed or unexposed. 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. Just as an example we work with a cohort called the Health Professionals follow up study. It was started in the 1,986 50,000 people who identified as men at the start of the study. They've been followed now for over 36 years. A case control study can be an efficient way of an alternative to a cohort study. But there are a lot more issues of bias. And you know, just when we think about what what things do we measure in a cohortStudy versus a case controlStudy? We often will measure. Another measure that you might see in epidemiology studies relate to either attributable fraction or population attributable fraction. So the idea is within the triple fraction. If you got rid of the exposure. Let's say it's smoking, let's says it's an occupational exposure, what proportion of the cases would be prevented versus in the entire population. The prevalence of well, let me talk about a trivial fraction first. So you're just looking at the exposed cases. What per proportion of those 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. You're going to have a much larger proportion of the cases. LZ: Can you think of a confounding factor that you might be worried about that? It's not physical activity. LZ: Yeah. alright. So let's talk about confounding. This is a real example actually of a project that I was working on with a student looking at physical activity and lung cancer. And this was a cohort of 40,000 women. 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. That's the risk factor, but that there's there's some additional factor that's correlated with physical activity. And on its own as a prospector for lung cancer. Body mass is a really interesting one for this. So by adjusting for smoking, actually, and what we did was first we adjusted for just ever smoking. But then, when you also adjust for the amount of cigarette smoked and the years someone smoked, the relative risk went almost to one meaning. There was no association between physical activity and lung cancer. Study looked at the association between coffee consumption and pancreatic cancer. If you drank one to 2 cups of coffee per day was 1.8, meaning an 80% higher risk compared to no drinking coffee, and if you drank 3 cups of coffees per day, it was 2.8. People who drank a lot of coffee were more likely to be smokers, and smoking is a risk factor for pancreatic cancer. So talk for a couple of minutes and think about given the design. Do you think it was causal adjusted for cigarette smoking they had just for other confounders, or what might it be? It could be a couple of things. like defining the expansion of copy not being shared with clocking conceptions that I think I said I just so could be. 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. So they're gonna recall things differently. The odds ratio essentially. The way you're calculating is what's the odds of exposure in the of the exposure, in the cases divided by the chances of exposure and control. That's sort of one way to think about the odds ratio. So you could have recall bias right? That is, these people are ruminating, and they're overreporting. The study found no association between coffee and pancreatic cancer. But the point that you just raised, which is a great one is. look at where they got the controls from. So they weren't able to get deal with recall bias. But we'll talk about, recall, recall bias in a second. 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. So he did this really cool design, which was, he had access to a cohort of nurses. There was a food frequency questionnaire that was asked and collected all sorts of information about the types of food someone ate. They were able to calculate different types of dietary fats from these foods, and then they followed people forward for breast cancer. So this was the cohort analysis. This is going to be in theory 3 of recall bias. The first column is looking at the Association of Total Fat Consumption of breast cancer risk, and then the second one specifically saturated fats in the risk. The first line of data is prospective cohort analysis. One is more of the case-controlled techno analysis. So what did they see in those 2 different approaches? And do you think this showed? Recall bias or not? Nurses may be more familiar even than a general population with the literature that, hey? There might be this connection between dietary, fat and breast cancer risk. So it could be a concern of recall bias in one population. Maybe it's more of an issue there, that's really interesting. In some cancer patients, when the cancer is more aggressive, can actually lead to weight loss. The weight loss, then, is a signal that you could use to detect pancreatic cancer earlier, some other things as well. So it's interesting to think of a bias actually being an advantage. 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. And then finally, I just wanted to raise in cancer. You know, we talk about confounding one of the strongest confounding factors can actually be screening right screening when you screen somebody for cancer. The office hour is going to be on next next Thursday after class, and it will be recorded so if people can't make it. Remember, at 50'clock today the Harvard canvas is gonna open. For which of the cancers you wanna work on and then finally, we're gonna put in the link. Trivial traction just refers to. only among the cases a proportion of the cases could prevent. And so I think the key difference with the population attributable is, instead, you're using the prevalence of the exposure in the full population. So, for example, if you were looking at, say, smoking and lung cancer.