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. You'll see which of the 4 of us that you'll wanna set up a meeting. 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. And I think my general sense is we did a deep dive and and talking to pathologists and basic scientists. Nobody really had a good answer. When you eat a lot of cooked tomato products, the lcapane constitutes in the prostate, and Dr. Jovanici, do you want to mention anything about your your study, your landmark study on tomatoes and prostate cancer? Well, I don't know, because Conrad Stopsack is giving the lecture this year. There's a small town in Spain which, right after the tomato harvest, they it started as a food fight, and now every year. And then a there it started many, many decades ago. And so first I wanted to kind of wrap up where we ended last week and sort of talk a little bit about this concept of time in cancer. When someone first has the exposure of interest, and ultimately, what when cancer occurs and that varies for the type of a cancer. 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. The incidence of breast cancer starts to increase around childbearing age. Around menopause, it still increases, but that rate of increase kind of slows down. And so, thinking about what factors might be playing a little in this part of the curve versus this one has been a lot of research. 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 prostate. It's interesting when you think about age again and thinking about puberty. height is associated strongly with an increased risk of many, many different types of cancers. And again, if you think about when children really start to grow, it's around that time of puberty. So when we're reading the literature or doing your own studies, you want to kind of take that into account. This is an interesting Analysis in radiation and cancer, and tried to understand what is the susceptibility of different tissues to radiation. Depending on age. And this is specifically looking at a range of studies that looked at different types of exposure to radiation and risk of breast cancer. This is called the excess relative risk. People who did not die as a result of the bombings were exposed at different ages. Children who were exposed early in life had the most strong association with future breast cancer risk. With time that excess risk is still there, but has attenuated substantially so. If someone instead was exposed at age 40 or 50, while there still is a small excess. 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. But certainly the bombing is long and sustained. Increased risk. Any questions about this? The latency is the period of time between when the first initiation happens and when cancer occurs. and a really strong example of this is in smoking and lung cancer. So what you can see they almost mirror each other exactly on the green line, looks at the increase in cigarette consumption over time among men in the United States. It was a randomized trial of low dose aspirin and cancer risk. The incidence is higher at the end of 18 years of follow up of compared to aspen. So the asthma is associated with a lower incidence of cancer. But what about the latency? When do you start seeing a potential lower risk in the aspirin group? How long did it take? The study looked at full weight, consumption, and the risk of colorectal cancer. The trial, the first, the follow up initially, was 8 years, suggesting there was no benefit of asthma. It wasn't until the 10 year mark when you start to see this departure, and it makes sense. The strongest association of Foli intake being associated with a lower risk of colorectal cancer, was in the 12 to 16 year lap. There's information on diet every 4 years, and so that allowed the researchers to estimate every4 years total, fully intake from diet or from supplements. latency is this concept of how much time between when the exposure first started. or when at least it was first measured. and the time when the cancer was actually diagnosed. 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. That's when you start to sees the benefit. But I think the way this analysis was done was specifically kind of what was your exposure at 12 to 16 years. Cancer is more common in men than in women and about 10 million cancer deaths occur each year. globally, over 19 million new cancer cases are diagnosed and we'll show in a moment. So I think that descriptive epidemiology is really interesting. It also is important, of course, in terms of the burden of cancer. This is based on data from 2,020. As I mentioned, the the burden of where cancer is occurring in the globe, differs by the type of cancer. This is just what percent of cancers are occurring in each region. And then on the right is cancer-specific deaths. 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. Take a minute. Why and talk about why. what factors might explain the total expected number of cancer cases and deaths. And are there some specific parts of the world, that we might be most concerned about once. 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. I think we just caught up again. Maybe it could be diagnosis methods improved. For example, diagnosis in the earlier stage of cancer. It could be a couple of different things. There's also, there's gonna be places where that had in general, like, you know, 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. So those things may be contributing to as well. 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, little more men than women. Ed was just recently awarded a research professor at the American Cancer Society, which is a very prestigious award congratulations. In the United States over, actually, I think the number now is over 17 million people are living as cancer survivors. 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. There's a lot of variability in standardized ways of collecting that information. For example, in Scandinavia, which we talked a little bit about, where it's actually mandated by law that all cancer diagnoses are reported at the national level. I think we have those issues as well in this country versus this country what I might be concerned about. I want to look at today. What are the most common incidents and mortality rates for cancer globally, and make some comparisons between men and women. Click on that link which will bring you to the global can data set. And then after that, you want to click on the multi bars. That you may wanna take a look at through group projects. The 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 through through screening right? So screening to identify cancer lesion before it becomes cancer. Lung cancer, mortality, colorectal cancer. Excuse me, skin is interesting. Many of the registers report melanoma. But don't report other types, squamous or Basil so and mo, and part of that is because those are. probably very high incidence, but not high mortality. Liver cancer was a little bit lower here, but because it's so highly fatal in terms of mortality rates per 100,000. It ranks quite high and then prostate. Cancer is pretty close to stomach cancer. You have some cancers like liver cancer, we can see the incidence almost mirrors mortality. Many people with prostate cancer died with their cancer, but not from their cancer. 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. So I think you'll learn a lot about your specific cancer. And then, as you bring it presentations together, and then when you present to the groups. You'll hopefully, I'll learn a lot. When do you think people stops big smoking cessation? Things started happening in the United States. So, therefore, smoking cessation in men probably started in the late. What about women? What are you saying in terms of the timing of when the increase happened? And then, when the decrease happened? There's a large difference in both incidence and mortality of cancer, by sex. The incidence is higher in men than it is in women. thyroid cancer is the one cancer that's higher in women than in men. The study used an ecologic approach and tried to adjust for differences, say, in smoking. So I know some of you were in my cancer course. So magic trick the whole course. But I'll try to cover today. And actually, since since I'm also teaching Thursday on obesity, physical activity, I probably won't get through all of these. So maybe the first 3 and I'll continue on Thursday. Diet is important for things like growth, and body weight. So so that that's under energy balance. Mediterranean diet, or like an inflammatory diet pattern which I'll talk about. And then what type of evidence should be prioritized to study died in cancer. Laurel. There are micro nutrients vitamins, minerals, calcium and 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. I have alcohol all here, but we could think of alcohol separately. There are other aspects of diet like, we don't think of carcinogens in general. When you cook meat particularly red meat, or you're not the kinds of me. And then, like contaminants, you can think of things like mercury and fish. II should also put like additives, for example, artificial sweeteners. Historical perspective is really important. A lot of people don't mention body weight or things like that, but they'll they'll mention things that you know where the evidence they're interesting. But the evidence, maybe, isn't that strong? Okay? So I think it's really important to know all this history. colon cancer rates from 1,964 to 1,995 these are men and women. So they went from about fivefold lower to twice as high, particularly men. which is dramatic, a dramatic change in about 3 decades. Dr. Song, Mignon will get into some of the specifics for colon cancer. There's a very strong correlation between fat intake and breast cancer mortality. Smoking alcohol could contribute in part to the men but smoking and alcohol is won't contribute for many to cancers in in Japan. And so so there. yeah, it's it's not doesn't directly link a specific dietary factor. But it's believed to be related. There are thousands of potential compounds that may be beneficial case control studies particularly indicated inverse associations with fruit and vegetable. There are other things like carotenoids laurel. I mentioned lycopene, which is in tomatoes,. which is an antioxidant. Ii just just for illustration that there are a lot of poly females. A lot of compounds that kind of look like this, and and they concentrate in certain foods. There are lots of compounds 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, and a lot of these are based on in vitro studies. But they're also like animal studies. The study was published in 1,990, and so I just took a few sentences from the abstract. So we conducted a combined analysis, the original data to evaluate the consistency of 12 case control studies of valued in breast cancer. Now, as I already mentioned, the dietary fats. But this is just to give you a spectrum of things. The study, along with other evidence like the ecologic stimulated this very massive women's health initiative, randomized randomized trial of a low, fat diet and breast cancer. So and I'll get back to that now in 1,981 Don Peto, or 2. 30% of cancers all cancer mortality would be prevented, preventable if everybody like and stop smoking or or didn't smoke. They had this very high estimate for diet. 35%, but also a very wide range. Now these, how do they come up with these estimates? th, they were. There's a wide variation in cancer rates, right? And so the US. Is up here. Assuming that this isn't all due to genetics, and there's reason to think that they're not in theory. Can, you know. can get down here in theory, like. maybe it's a reduction in fat intake. But there's there's something probably related to diet. There was actually very little data at the time on things like obesity, energy, balance, fiscal. So so then they made some estimates for specific cancer types. And then they said, although this figure of 35 is a plausible total. The parts that contribute to it are uncertain in the extreme. "They were so precious, I mean, I remember, like in their paper they they said like, well, there isn't much evidence for over nutrition, except for endometrial cancer at the time, but like, we wouldn't be surprised in the future if more studies more evidence emerges on the importance of over nutrition" Vitamin trace elements, micronutrients protease inhibitors or antioxidants that finish up in the top. 12 hypotheses might just be testable. as might intake of various putative, influen protected types of fat or fiber. If one of them hits, if one out of 10 hits. that's great, you just help, you know, the population to eat more of that. If you're focusing on a micronutrient why not do a randomized trial, right? That's you'd get a very definitive answer. So that's how the field kind of was thinking at the time. And so for the actually that that gets into this next part, which I'll talk about is is that you know it does make sense. There was a lot of interest. There's not much interest that I know nowadays. It's just a compound like that may have anti-cancer effects. That's part of all the micronutrients in that child exists. Yeah, there's I forget exactly how they work like they they block certain kinds of enzymes. 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. There are issues like. latency is one of the issues that we'll talk about. But but the bottom line is, let's just find a bunch of compounds and then do randomized trials. Double blinded study is feasible in most cases for diet and cancer. But if you're looking at, you know, diet 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. Diet can affect other cancers and other diseases. You can't ignore that information for ethical reasons. It's hard sometimes to do like a placebo control. The 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. There have been attempts to have like these big changes in the diet like low, fat diary pattern. And those studies had very big issues with compliance. It's very hard to get 30,000 people to have massive changes in your diets. So diet and cancer, you know, it's very difficult. There are lots of issues that that could lead you to get the false or misleading answer. Cancer occurs in stages, and you know this is sure to some degree simplify, but I think still useful. So it's a very has like different stages. This isn't trial data. This is observational data. Actually, the nurse's health study. When you look at colon cancer and years of multivitamin use of. you see, like not much going on, certainly, after one to 4 years, and then perhaps suggested a not significant reduction like 5 to 14 years, but then a clear lower risk. Now, aspirin is protective. It's going to be a while to see an effect, because, like one way, I think the simplest way that that I can think about it is so. If if you have so the cancers you're going to see at 60, like the last. the previous 10 years have have nothing to do with initiation. People who have children at a later age since you mentioned that these cancers developments in the initiation started on 50. So, for instance, someone had children at age 55, is it possible that their mutated genes for the child. At an earlier age they will have less damaged genes in later age. 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, that, like age of like the father, I think older age would have a higher risk of that. So that's a related but another issue, like in terms of what's passed on the term line. The group that starts with twice as many initiated cells probably is going to have twice the risk of cancer. So you have twice a number of initiated cells, and then over the next 50 years, lots of things have to happen, exposed the estrogens. but they're still far away from cancer. There is an inverse association between calcium intake and colorectal cancer. Starting from low calcium intake as you go high, the risk gets lower, and then it levels off. If you're like a 1,300 milligrams today, going to 2,000 doesn't seem to be that beneficial right? The women in the trial were already taking, but on average, 1,150 milligrams of calcium. And and they even reported that their diet intake even went up over the trial. So it's almost like calcium deficiency increases risk of colon cancer. I mean there could be ethic. I'm not saying necessarily do this ethically, but you would ideally do it. A trial with like people were low in calcium. So then you give them calcium, and then they may actually benefit. But if they're already getting tons of calcium, they're probably not gonna benefit. So that's something in nutrition that you have to think about like you don't think about that in like a drug. Alpha Tacophile and beta carotene have antioxidant properties. So they said, You know, like, Wow, maybe all this benefit of like fruits and vegetables, or a lot of it is due to betaCarotene. But it's like, How do you generalize the finding? Alfred teferall didn't work prevent lyme cancer. Vitamin e alpha taco, or Beta and Beta and see if it's protective. Within about 6, you know, 7 years, about 4% are accumulated like lung cancer. 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 a placebo. Beta Carotene is not neutral. It's actually bad fuel. The high is people who really like carrots and orange stuff oranges things like that. The low is those who don't eat fruits and vegetables. Fruits and vegetables associated with with some cancers. Lower risk of some cancers in case control studies, fruits and vegetables are high in antioxidants. So so so this is kinda summarizes like his, like kind of my take on that Atpc trial. So the the men were getting so much Beta Carotene that so a lot of them actually knew that they were getting BetaCarotene set up Placebo. Antioxidants Beta Carotene and Alpha Cartherol, Antioxidants there were actually just. but were really interested at the time, you know, because people were just learning about vitamin a and vitamin e, so there could be thousands of compounds and fruits and vegetables, but they focused on these 2. A dose of synthetic Beta Carotene 10 to 20 times higher than the natural diets and extremely heavy lifelong smokers. A lot of these men already have these advanced free cancerous lesions more or lung cancer risk with 5 years. The trial may have asked an interesting question, but has it really addressed the top question in terms of value?