Conrad is a physician, scientist trained in internal medicine, received his MPH here at the Harvard School of Public Health. Conrad 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 here at Harvard school of Public health. In the second part, if you will, are the things that talk about, what can we do about this? And the first one is risk factors and primary prevention. And then we'll talk about the descriptive epidemiology. How much of prostate cancer is there, and particularly racial disparities in prostate cancer. Prostate cancer is one of the most common cancers in the human body. The prostate is hidden in the pelvis, next to the bladder and the rectum. The urethra goes directly through the prostate and the other condition there is is prostateis, but other than that, it's such 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? So that's staging? That's similar to what you see in in other solid tumors. And we'll also talk about grade. Which basically means, how does the tumor look like under the microscope? 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 third is the tumor already having spread beyond the prostate. 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. If we look at relative survival in the in 5 years after diagnosis for those 70% of patients diagnosed with localized prostate cancer. 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. And so that means, if people who get a diagnosis of prostate cancer are more healthy, the relative survival will be better. The survival of metastatic prostate cancer is poor and continues to be poor, and there is no curative therapy for it. Cancer is a big public health burden. So it's really about different people getting getting diagnosed. but not to forget. But there is a different second aspect to sort of one of the 2 big perspectives on prostate cancer. The organizing pattern of this tissue is really very clear, and as cancer progresses or as cancer initiates and then progresses through its grades, the tissue becomes increasingly disorganized. We would be creating 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. The prevalence of prostate cancer at autopsy. of men who died from other reasons than prostate cancer. The scale here goes from 0 to 60%. And these are the 3 bars are for different racial categorizations. What do you make out of this data? And what do they tell you about prostate cancer? The prevalence of toxic cancer at autopsy already goes up to very high levels for 30 to 39 year olds. White European populations between 29 to 30 to39. Not offering the treatment or the screening tools in that population. That's why they are having diagnosis. It's just chain also issue. Life expectancy is a lot shorter in black men in the United States. The other one is, there were just fewer studies also. So the data weren't sufficient to come up with reasonably precise estimates for that group. But prostate cancer. yeah, what do you think? What could be going on there? 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 we auto seed everyone, we're not doing that. There is way, more plastic cancer that could be diagnosed than what we are, even currently with very intensive screening diagnosed. So of these huge prevalence numbers here the majority will remain undiagnosed. There are 1.4 million. About incident, prostate cancers globally with very strong differences by both our continent and by a country with particularly notable. Lower incidence rates in Asia. 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. I think that's the most important pattern to to point out here. And then for prostate cancer mortality a different. broader picture, with particularly notable high mortality rates in sub Saharan Africa and in the Caribbean and again. relatively low mortality rates in Asia. The Psa test is actually not a bad test, but it's not been used very smartly. What people are doing exactly to your point is, they're integrating information from additional tests. We hope to see better, smarter testing in the next few years. To mention the Psea test will remain part of the mix. US Preventative services task force recommended against prostate cancer screening. In 2015, they changed course and recommended screening again. So then, you see incidents going up again. Those are the major factors in fluids. Of course there's more going on here, but those are the main factors. There's the stark difference between the black and the curve for black and for for white men here for the United States. There's the uptake of that the changes weren't as dramatic in the in the lower. That's apparent. Anything else? Very maybe jumping at you when we look at the 2 curves. There are huge changes actually up to 5 fold in the same country of prostate cancer mortality rates. And we're we're more notable in in the in the back group. The absolute number of deaths was a lot higher that were prevented among flattened. Why could that be? Because I don't know the answer. Medical care changes our ability to even diagnose it. We're splitting up the same disease into into more than more and more categories. So I think that's a great explanation. That is certainly one. And we see such changes for other cancers, too, not always in the same direction, with the same patterns. In a town on the eastern border of Germany, called Garlitz, on in 1,987. There were 1,060 people who died in that town of Gurlitt. Prostate cancer is a cause of death. But it may not be the only explanation other. Currently, 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. And of course they did that here, basically for research purposes. Of those 199 people, 178 were found to have died of cancer on their autopsy. So actually a pretty high, positive, predicted value. They didn't have computer tomography. There was no Psa. There were lots of things this in just pass it, of course, but there was lots of medical care that wasn't available. There is definitely room for some of the differences over time if medical care gets more accurate to explain these things. But it doesn't seem like we're not seeing that the majority of cancer causes on the death certificate were wrong, at least in the in one town in Eastern Europe. In theory, Germany, a well resourced country and so forth. This was Eastern Germany before the reunification services behind the Iron Curtain. The death certificate may not reflect the entirety of what we know about them medically, even in life. I have anecdotal answers for this death. Cancer creates havoc in the body in terms of blood clots, for example, and that causes a polyamorous one. That's what people ultimately die of, but that is the immediate cause of death, and it shouldn't be the one on the death certificate, because people would not have had. The underlying cause of death is actually cancer. That's how ICT classifications of death are to be performed, says the who. So, for example, during the COVID-19 pandemic. There was a lot of arguments about is CO VID-19, a common cause. 300,000 people are expected to be diagnosed with prostate cancer in the United States this year. About 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. Will have a diagnosis of prostate cancer. We don't exactly know how many are actually living right now with metastatic prostate cancer. But about 100,000 to 150,000 of them. If White were the reference group than the mortality rate in black men were 2.1 fold greater. But if Asian were and Pacific Islanders in one group were thereference category. Then we're talking about a fourfold difference. Migrants a generation later are genetically the same as the country they're coming from. lifestyle factors. Migrant study where. looking at prostate cancer incidence before psa screening messed up the picture between. the first generation of migrants to Hawaii, the second generation and white Hawaiians. Stomach cancer is the major modifiable factor for stomach cancer with hygiene and more antibiotic exposure on immigration. What about breast and prostate. Even within 2 generations, for both breast or prostate cancer the levels of risk don't reach that of the of the other archbishop. That is summary that everyone more or less could agree with. Men who have a brother or a father who has a diagnosis of prostate cancer have a 2 to 4 fold higher risk of cancer themselves. Men with a mother or sister with breast cancer, breast cancer have 1.5 to 1 point sevenfold higher risk. Plastic cancer and melanoma are the most heritable cancers due to genetic factors. The Y axis shows us something that we'll see in the next few slides is how much of that genetic risk can we already, with genetics from today explain this? Actually, the number has actually slightly increased since this slide. And I'll show you the latest numbers when we talk about genetics. We all have common genetic variation, because that reference genome is not a real person. And the effects of those common things that are slightly different between people. 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 quite useful for risk stratification. There are 451 variants, single nucleotide polymorphisms or snps for prostate cancer risk. Some of them with a P value of 10 to the minus 600. The effects of each variant are very small, so that P value is really driven a lot by the fact that we have huge sample sizes. Vast majority of prostate cancer is happening among people with polygenic risk score above the media. 40% of the population has a very, very low risk. A diagnosis is sort of would think comes before death. So people who don't get diagnoses of cancer also don't die from us. 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 where they don't perform as well. 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. There are lots of functional studies, but there's nothing magic about there being exactly that number. Auc is a model that looks at how many snps make the statistical significance threshold. And, as you can see, 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, the Auc got better. But it doesn't mean that these things here 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. If you haven't voted yet, please do. And then we can give God. There is common genetic variation, and then there is rare genetic variation. So it's likely that it's not all common genetic variants. But there is. There is. And so that's great to see. And does anyone want to give the motivation for? Why you picked that answer and not the others? There are things like Rocket, one, Brachit, 2, and so forth. And they're they're not rare there there as causes of cancer, 10% of cancers are probably caused by them. So that's why this is actually a thought. I'm giving you the right answer. At least, I thought. This is the one where it tricked you with a with a confidence and I'd love to walk you through. The genes and the environment don't sum up to 100%. 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 every condition is always so. I don't know if cosmic radiation causes prostate cancer, you won't be able to say that's not the case. Cosmic variation is responsible for 100%. And Ips, a genetic factor is too. And we can even act on these. We could maybe eliminate cosmic radiation, which is nonsense. but that would get rid of all of it. or we could. We may have better interventions that people with a particular genetic condition benefit from. Germline variants increase the risk of prostate cancer, but non genetic factors increase particularly the risk. We have more shots at cancer prevention. And one concept that we'll talk about is there's indolent. And there's aggressive prostate cancer. And then we can screen to reduce the stage of diagnosis. 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. And then there are issues around treatment, access per and all of these things are relevant, not just for prevention in general, but particularly also for reducing racial disparities. height is a strong risk factor for prostate cancer. And actually, other cancers, too. African descent and genetic risk close but are separated. While during puberty, so very early in life, both genetic and environmental conditions can play a role in the development of a cancer. There's often a long time between when somebody is exposed and when we see the effect of an exposure. So how much food is available, what kind of food, how much dairy do people consume? Those things do influence on bike gain, and they also influence presumably the growth of the prostate. And we've seen that they influence the risk of prostitute. If we did that, if we threw them all into one bucket as risk factors. Out of that bucket would come age, race, and family history. Maybe we would get a few other risk factors because they're very, very strong risk. And they would be saying something like, Don't know exactly. Put something down there. Being pregnant more often decreases the risk of basically hormone receptor, positive breast cancers. But it increases the chance of triple negative breast cancer. And if we throw all breast cancer into one bucket. we put Cnola Association. Oh. we still throw mostly prostate cancer all into one. bucket. People who are interested in health maintenance are healthier and psa screening detects certain types of prostate cancers better than others. When we talk about cancers that have the potential to metastasize, then that is a different subset, and these are possible or probable risk factors. And all of a sudden that list gets a lot longer. The gene fusion between 2 genes er g and tempus 2 is about present in what half of all prostate cancer. Across quintiles of vigorous physical activity the association with urb negative prostate cancers is completely null. There is at least the suggestion of a protective association among erg positive prostate cancers. The results are even stronger among men who were all undergoing Psp screening. I would particularly want to look among highly grief men as opposed to just everyone intend to be wild. Because the in Egypt. you know, protected behaviors like they would like to reduce the risk. 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 maybe preventing prostate cancer could be masked by that. If you screen at regular intervals you're more likely to pick up a cancer that has been sitting there all alone. The lifetime risk of any prostate cancer type is something about 15% and goes up to 50% among people in the highest quartile. So death, comprising cancer or substantial differences by genetic predisposition, just common genetic variants developed. So I said, this is one example of a healthy lifestyle score, so very very basic things in a way very leniently defined. 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. We can't make this go away and like it's been seen in other studies. This is not a result just for prostate cancer. Psa is just a biomarker. It's a protein that's made by prostate. People at a high genetic risk are just as amenable to, or might benefit in relative terms just as much 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. Initially, Psa was meant to be a marker just for measuring progression of prostate cancer. It was quickly repurposed for screening, for prostate cancer, which is a much bigger market. 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. The American trial showed that it didn't work. But it turned out over the years that actually the American trial had not worked. But nobody should get screened if they don't have access to treatment, because then we're only harmed. The numbers needed to invite and to diagnose or higher. get them at first, but they're actually very similar to breast cancer. This is how mammography screening looks like, too. And this is then the number of people who need to be treated in order to prevent one death from this specific cost. 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. And incidence actually goes, though, this is a test that detects cancer. So it makes incidence go up. Prostate cancer mortality may not be continuum. Task force has been going back and forth about whether screening is recommended. This relative survival is where we where we started. We started with relative survival of prostate cancer in the 1,900 seventys around 70 to 70%. And now it's at 99%. 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. Risk factors along the life course have an effect on to the risk. This is a cancer that really still needs a lot of work. insulin and growth factors. both during puberty as well as for the other risk. factors during the life course have a big impact. Psea screening. It reduces on prostate cancer mortality and really profoundly impacts the observed burden of prostate cancer. As always, we've looked at prostate cancer very early in life, that it is a disease of older men.