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. Everyone is due at the same time. But we did put up the schedule, so you should all know and be prepared. 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 that's totally fine. If you do it in less than 2, that's awesome. So yeah. any other questions cool. Heather Pi is a world leader in the epidemiology of breast cancer. She's Pi, the principal investigator nurses, one and 2. She did a nice interview of the Harvard Magazine, so I think we put an attachment on it. Course websites react to one. So that's a very nice thing to do. CNN.com Live is a weekly Newsquiz where we test your knowledge of stories you saw on CNN.com. Today, we'll be talking about breast cancer. Go to this QR code and I would love to hear you can put in just a risk factor for breast cancer that comes to mind. We're going to talk about a lot of these today, and if we don't talk about them, and you have questions about any of these that you've put in, or that others have put in. So just as an overview, we'll go through a little bit of descriptive and epidemiology, and then go through risk factors. Think about reproductive factors. Black and Hispanic women are more likely to be diagnosed with breast cancer than white women. How endogenous hormones fits into this and underlies a lot of the risk factors risk factors that are modifiable or potentially modifiable, and then talk about mammographic density risk prediction. I actually took out because I didn't think we would have enough time. Women are more likely to be diagnosed with breast cancer and to die of breast cancer than white women. Black women have the highest mortality rates the fourth black and Hispanic women have higher breast cancer mortality rates. So see, see what you think about this. and then we'll go through a bit of the descriptive epidemiology. More screening might be detecting more cases of breast cancer. What else might differ obesity, obesity. Less developed countries die younger. You do other causes rather than developing cancer. Infectious causes. So potentially that shift between communicable diseases having a bigger impact and then noncommunicable diseases. Study looked at how rates of breast cancer change with immigration. It really highlights that it's not all genetics being the difference. Japanese immigrants in Hawaii and in San Francisco compared to the top, solid red being whites in San San Francisco. So but some of the things that you're all getting at are the fact that there are things other than genetics that differ. So there are different patterns or risk factors. There's a difference in the mortality patterns across the globe. The more Westernized countries at the top with a higher incidence rates. And so you can see that as people move and spend more time in this country they end up adopting the rates of the higher incidence rate of the whites in the country. 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 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. I'm just in that age group of like 60, 60 more, I mean the steep is higher. Breast cancer rates have gone down in women in the Us. Smoking's not a huge risk factor for breast cancer rates. There have been changes in lifestyle changes in the risk factors. There has been a sharp increase in the Dcis in the eightys and early ninetys. 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. And in fact, this, this deeper increase in Dcis. These are very small tumors that are not easy to detect by lumps. In postmenopausal women, thousands and thousands of women stopped taking hormone therapy. And we can actually see that change in the breast cancer incidence. We'll go through hormone therapy in its relationship with breast cancer. But I think these curves, we tend to think, why is breast cancer increasing over time? But you can actuallysee increases and decreases related to particular events. The different subtypes of breast cancer have very different outcomes in terms of prognosis. And I think that this is probably something that you've talked about in relation to other cancers. One way of looking at this was by using gene expression and categorizing breast tumors by common gene expression patterns. This is something that went from being a prognostic indicator of poor prognosis to becoming an indicator of a tumor that's going to respond to a very effective treatment. But nonetheless, it shows you that these molecular subtypes actually do have meaning in terms of what the natural history of the disease and the outcomes could be. These are all under er positive, and they get split a little bit into luminal A in limital b, and then under the er negative, we have the her 2 enriched. 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. On the left side, this is looking at breast cancer, incidence and death. By race and ethnicity. So if we look at black versus white. In terms of mortality. What do we see? Right? So the mortality rates are higher in black women. Right? Yup. Black women have a higher proportion of their breast. Tumors are these triple negative tumors. and they have a worse prognosis. So triple-negative tumors. And so, if you compare these distributions between white and black women, what do we see but someone from this side of the room. Negative tumors are harder to treat, and they're more aggressive. We don't have a very good target therapy for so the hormone receptor doesn't express an estrogen receptor. And so a lot of these patterns are going together, contributing to the difference in mortality rates. There are lots of potential differences in structural access to care, treatment, screening all of these things can also be contributing to some of the disparities that we're observing. But there are also some molecular differences that are adding to that as well any questions on this. One of the reasons is that they tend to have more breast cancers at younger ages. Some of it could be related to the fact that we'll get into some of the reproductive factors. After pregnancy, the the risk of breast cancer increases for a window of 5 to 7 to 10 years after a pregnancy. Those tumors are slightly more likely to be triple negative tumors. Breast cancer survival rates are higher than those of other cancers. Five-year survival rates for breast cancer are 90%. For pancreatic cancer, the five-year rate is less than one in five. There may be other differences contributing to the higher survival rates. But it's a good question. Other questions. There tend to be later recurrences, causing death, 10 to 15 to 20 years after the initial diagnosis of breast cancer. And it's a big question of why does this happen. Why is it that these tumors recur much later? And what can we do about it? The overall breast cancer survival is very good. Most women who are diagnosed with breast cancer end up dying of another cause. But there is a significant breast cancer, death. How can we try to prevent some of those occurrences so overall great survival rates, but still a lot to be figured out and potential places to intervene. 5 year survival rates for white women is 92% and 83% in black women. And here you can look at the differences by whether the tumor is localized or has spread regionally or more distantly. This does not account for molecular subtypes, but I think if you adjust for those molecular subtype, you still see that there's a disparity in the survival between black women and white women. Men do get breast cancer, but it is predominantly showing up in women. There are inherited mutations that carry a very high risk of breast cancer over lifetime. benign breast disease is something that is now more commonly detected, thanks to mammography. Later we'll get into endogenous hormones. There are risk factors that occur across the life course. Breastfeeding is associated with lower risk radiation. When you have radiation to the chest increases, risk. mammographic density which you can detect on a mammogram will go through exogenous hormones. We've already talked about hormone therapy, and we'll get into a little more detail alcohol, adipocy and physical activity. This is sort of a conceptual model that was put together from a working group looking at environmental factors and their impact on breast cancer. So you think about going through gestation, puberty, and then pregnancy and lactation. And so at each of these developmental stages there are chances that risk factors could be having an impact on the development of the breast tissue. Evidence suggests that childhood and puberty are a particular window of susceptibility, for breast cancer. And then the rainbow is representing the fact that etiologic factors could come into play at multiple levels of thinking of the biology as well as behavioral and social levels that could be playing a role. Women exposed in their 30s, 40s and 50s had not much of an elevation of risk of breast cancer compared to the women who were exposed when they were children, or in their teens or twentys. This really highlights for us that something really important is going on in the breast issue at that time. Looking at childhood weight is something that shows up as being a breast cancer risk factor, but potentially not in the direction you were thinking. The way we've gotten at this in several studies is by asking, women call their body size or their body shape when they were different ages in childhood. And so it actually validates quite well. The higher the rescue way that the smaller the rate of breast cancer. It starts from the beginning, starts after the first to measurements or system. So to me this is really striking, not only the inverse association, but the fact that it's something that lasts for many, many decades. So what a woman's body size was in in adolescence is impacting risk of cancer in her. In postmenopausal women. Childhood adiposity seems to be associated with lower risk of of both types of tumors. And it's really pretty striking, also a very hard message to think about with public health. This is not the message that we're thinking is the right thing to pass along. Age at monarchy is a pretty well established risk factor for breast cancer, and this shows decreasing risk with every year later that monarchy occurs. So we do see that it's associated with mammographic density. And so again, I think there's something about establishing. It's changing the breast tissue at that very early age and having some impact. The longer monarchy, that initiation of Menzies is delayed, the lower the risk of breast cancer. If overweight, girls are more likely to have an earlier period or a later period when they first start. So these 2 go a little bit at odds. They're not going in the same direction. And yet both of these are pretty strong. The earlier monarchy starts the earlier you start on this you know, big curve of being exposed to estrogen estradial over the life course. So thinking about age, at monarchy. So one thing that has changed, you can see the Bmi in young adulthood is associated with. an earlier monarchy. The average age of a woman in the UK is now 1211, down from 1716. This is a much slower change than perhaps the obesity epidemic. But it is nonetheless contributing to potential changes in breast cancer incidents, says Dr Michael. He says we can look at diet and lifestyle in childhood and try to understand whether those have an impact on cancer. There are some shifts in our diet and lifestyle habits that are contributing to some of those shifts in monarchy as well, and probably lots of other aspects of the way our lives have changed, too. It's an interesting one. 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 reduce the risk of breast cancer. Eating grants and system childhood adiposity doesn't increase the risk. No agent! Oh, agent monarchy! So that's a good question. And I don't know that it's been picked up as a risk factor for other cancers, at least not strongly. Women who have more pregnancies have a lower risk of breast cancer. But if the woman who had her first birth at age 35, and then had 2 more children, she still would be at an elevated risk. It's a great point, though. Maybe, that those who had pregnancy at the younger age also had pregnancies. Right? The breast tissue undergoes tremendous change with pregnancy and birth and lactation. So you can think about a later age at first birth has more time between monarchy and the time of the birth, so that breast tissue develops. So we talked about those windows of susceptibility and what's going on in the breast tissue. Pregnancy throws all these hormones at the breast tissue, and can contribute to replicating some of those mutations that have been accumulated. 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. So breastfeeding or lactation has shown pretty consistent evidence across many studies that breastfeeding is associated with a lower risk of breast cancer. And it does seem to be dose dependent. independent of parity. 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 nice thing to be able to see. The earlier you go through Menarche, the earlier you start that large exposure to circulating estrogens. The later an age at menopause is, the more it stretches out that exposure to high levels of Estradiol. And you can see this particularly contrasting a woman who has a bilateral efrectomy. So both of her ovaries removed before the age of 45, has about half of the risk. Early monarchy is not associated with early menopause. It's just a question of you can have variation in both spectrum. The longer you have that reproductive span, the higher the risk of breast cancer. But you see that early days so early monarchy isn't associated with early menopsause. But it's usually independent of monarchy. There's been a lot of interest in this for women who have infertility and does the infertility impact breast cancer risk. And if women have infertility treatment, does that impact breast Cancer risk? And there's been 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. So many nuances in breast cancer. Do you have any experiences? Right? The risk model here actually takes into account the spacing of the birth. So there is some impact there that a woman who had a birth at 20 to 23 has a lower risk. But that 20 to 35 is still not as high as this 35 year old, because she'd been through the pregnancy early at age 20. Hormones are acting as growth factors, and this increases opportunity for replicating a mutation that already exists in the tissue. There's also the possibility that estrogens could be contributing to cancer through genotoxic mechanisms. So they can actually create atoms in the DNA and contribute to damaging the DNA. When estrogens and progesterones are high in the ludal phase, you can see that the mitotic rate, the rate of division of these cells in the breast. Epithelium is higher at that point. So this was a good hypothesis that these hormones are contributing to proliferation. Women who tend to be on the higher range of normal for circulating estrogens have a higher risk of breast cancer. Women who are on the low end of the estrogen spectrum have a lower risk of the disease, according to the study. The study was pooled with other studies of pre-monopausal circulating hormones. In premenopausal women, most of the estrogen is produced in the ovaries which can then impact the breast tissue. The ovaries no longer produce estrogens, but they keep producing androgens. And what happens is those androgens actually get converted into estrogens in the adipose tissue. So in postmenopausal. women, those circulating estrogen levels which are much lower than they were in pre menopause. Women who are in the top 20 to 40% of those circulating levels are at a higher risk of breast cancer. So estridiol and estroan, sulphate as well as testosterone. circulating androgen levels are also associated associated with higher risk in postmenopausal women. We see that it's similarly predictive of higher risk, independent of some of these other risk factors. So as we talked about, we'll get into a little bit of some modifiable factors. But you can think about how these relationships with the circulating hormones may be related to some of the factors we're going to talk about. As a woman enters menopause, the adipose tissue that she's carrying is contributing to those circulating hormones. So you end up seeing a higher risk of breast cancer in the obese woman and the lean women end up, then switching to having a lower risk. But it's, in fact, on the low end that occurs. This is a more recent pooled analysis that pulls together many, many studies, including our health study and nurses. So this is looking at Bmi between 35, and 44. And you can see this very consistent dose response relationship between increasing Bmi at these ages and lower risk of breast cancer. Even when we adjust for childhood out of posterity, we still see this relationship, that it's an inverse association with breast cancer risk. But then it changes again as we saw in that first curve, it changes with menopause. So looking at overweight afterMenopause, this is looking at weight change since age 18. Women who lose weight after menopause are at a lower risk of breast cancer, study finds. Women who are not taking hormone therapy are at an increased risk of developing the disease. The study suggests that adiposity is contributing to risk likely through a hormonal pathway, according to the authors of the study. Hormone therapy is contributing to lower estrogen levels overall. It doesn't matter whether it's intentional or not intentional. Use so estrogen plus progestin for less than 5 years, and then this is estrogenplus proges. Use of men, pausal, hormone therapy, and it increases with longer duration. There are a lot of differences between the randomized trial and observational studies. For more than 5 years now we do see in our cohorts an increased risk with estrogen alone, whereas women's health initiative, actually saw an inverse association. And then you can see here this is again this large pool of analysis, looking at estrogen plus progestin. Once women go off hormones, as we saw in that decline in the incidence of breast cancer over time, they have a lower risk. So you can think about it as you go off hormone therapy, and it sort of puts the brakes on whatever in terms of growth, being fueled by those hormones. The impact of endogenous circulating hormones from higher Bmi versus adding, exogenous hormone therapy and looking at the impact on breast cancer? All right. Just the to the presence of prisons. Vary on. If it's brca, one or 20, great question. It does so. 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, absolute risk. After people stop using the risk declines so that there's 10 years after stopping oral contraceptives, there's no increased risk. Alcohol is a very consistent modest but consistent risk factor. 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. So we can measure this in the blood about a 15 to 20% reduction in breast cancer risk for women in the top. Fifth, compared to the bottom. Women who were not very physically active before menopause had a lower risk of breast cancer compared to women who were consistently low physical activity. So here's sort of a summary of thinking about the impact of modifiable factors. So adiposity, menopausal, hormone, therapy, alcohol, physical activity and breastfeeding. Mammographic density well established, positive association between mammographic density and breast cancer risks. There's legislation now that requires women to be informed whether they have dense breasts on a mammogram. So it's pretty striking a fivefold increased risk for women who are in the top quartile of density compared to women in the bottom, having no breast density. Dense breasts are much harder to find a tumor in compared to fatty breast tissue. 10 years later women who, with dense breasts have a higher risk of breast cancer. It's not just masking an existing tumor is the use of ultrasound and MRI chained. Yet. There's still some that are gonna be hard to detect. We see a mammographic density associated with both er negative and er positive. So maybe this is actually lower, because we're detecting them better if they get moved on to the next step. And that's a great question. I actually don't know that it's possible. The relationship between adiposity and breast cancer risk, we're picking up through a mammographic density relationship. So we've been working with some colleagues at Mit and at Mass general who are using AI tools to develop or to get more information out of the mammogram. So, reading the pixels at a much finer level and finding that there is more information. Lower Bmi. agent, monarchy, great. Another audacity. In early life. Monarchy. obesity great. Not so straightforward in breast cancer. But thinking about what's going on early in life is is new for a lot of you, and it's pretty fascinating. I wish we had better answers to try to tease it apart.