Unraveling the Complexities of BRCA-Related Breast and Ovarian Cancers

The BRCA1 (BReast CAncer gene 1) and BRCA2 are genes that produce proteins crucial for DNA repair. Since these proteins play a pivotal role in cellular resilience against DNA damage — mutations leading to inactivation of these genes results in increased vulnerability to cancers. Women with inactivating mutations in BRCA genes face elevated lifetime risks of recurrent breast and ovarian cancers, often having to undergo vigilant monitoring with some having to opt for preventive surgeries to remove their breasts and ovaries to reduce cancer risks. Despite advancements in understanding the initial cancer development, the factors driving recurrence of BRCA related breast and ovarian cancers remain elusive, posing a significant challenge in managing the long-term health of mutation carriers. We are talking to Dr. Katherine L. Nathanson of the University of Pennsylvania to understand more about the complexities of BRCA related breast & ovarian cancers and gain insights into ongoing research and the potential avenues for future breakthroughs.

Full Transcript:

Shweta Mishra: Hello and welcome to Curetalks. Today we are talking about the Complexities of BRCA-Related Breast and Ovarian Cancers. I'm Shweta Mishra and we have with us today, Dr. Katherine Nathanson, Pearl Basser Professor for BRCA-related research and Deputy Director at the Abramson Cancer Center and Director of genetics at Basser Research Center at the University of Pennsylvania. Joining Dr. Nathanson on the panel is Heidi Floyd who is a sought-after influencer with over 10 years of experience in healthcare advocacy and breast cancer nonprofit management, and she's also an international speaker and a published author. Welcome to Curetalks Dr. Nathanson and Heidi. It's a pleasure to have you here in the panel today.

Dr. Katherine Nathanson: Thanks so much for having me. Looking forward to the discussion.

Shweta Mishra: Thank you. So, Dr. Nathanson, we know that there are a number of inherited mutated genes that can increase the likelihood of breast cancers and the most well-known are the BRCA 1 and 2, so I would request you to start by giving us a bit of a background on how BRCA 1 and 2 genes are related to breast and ovarian cancers and touch upon the mechanisms of how these cancers develop?

Dr. Katherine Nathanson: Sure. So, BRCA1 and BRCA2 when mutated are associated with increased risk of predominantly breast, ovarian, pancreatic and prostate cancers. It's thought that the increased risk comes from the fact that they are associated with homologous repair deficiency or DNA damage repair – I am trying to think of how to simply put that – sort of repair of your DNA – and so when you have a mutation in BRCA1 or 2, everyone has two copies of the gene but then you have one copy that's not functional and you can survive fine and do totally fine with just one copy that's functional on your cells. But if a second copy is lost then that loss of both copies in the same cell can be predispose to cancer. We know that women who have BRCA1 and 2 mutations have an increased risk of breast and ovarian cancer. There have been studies both family-based studies and more recently sort of population-based studies that have really looked at that increased risk. And again, depending on the study the risk ratio obviously varies, although we like to look at the sort of population-based risk and sort of think about it as more or so of probably 50% 60% sort of lifetime risk. Again, there's a range of risk for breast cancer, it's lower for the other cancer types. We actually interestingly enough don't know why it's breast and ovarian cancer specifically. So, what's called tissue trophotropism. Why are the specific mutations in those particular tissues that are associated with cancer, it's not really actually really well understood to this day. Patients particularly with BRCA2 mutations can get a variety of other cancers as well. But many of them have a sort of somewhat increased risk over the population but not to the degree of breast and ovarian cancer, but we haven't really quite figured out why

that risk is particularly higher in those tissues, but we certainly know with many many people and many many large epidemiological studies that that's the case.

Shweta Mishra: Thank you for sharing that Doctor, and could you talk a bit more about the inheritance of these defective and harmful BRCA genes so we can understand who is at risk of having these genes and who should get tested?

Dr. Katherine Nathanson: So, the inheritance is what we call autosomal dominant. So if, you have a parent who carries one of these genes. Then you're a 50% risk of inheriting the chain and that 50% is independent for each child. So, it's like flipping a coin for each child and having done this for a while I've seen families with four people no one gets the mutation, four children, everyone gets the mutation. That's really a random flip of the coin and so that's again the Inheritance. We know that the mutations themselves are really more frequent, in certain population there are some founder effects. For example, the West known or the Ashkenazi Jewish population was about 1 in 40 individuals who carry a mutation in either BRCA1 and BRCA2 probably because they went through what's called a population bottleneck that is their population got smaller, there's only a few founders and then that number of populations expanded and so that was true. But the Ashkenazi Jews are by far enough the only population. There are other populations that have an increased rate just based on sort of founder effects. That's true for other mutations in other genes besides BRCA1 and 2, but we're just specifically talking about BRCA1 and 2.

Shweta Mishra: Right. Thank you, for sharing that in an understandable way doctor and you did mention that these cancers which are related to BRCA have a high rate of recurrence and you in your research have discovered factors that make breast and ovarian cancers associated with BRCA1 and 2 mutations more likely to occur, right? So, could you please break it down for us in more simpler terms?

Dr. Katherine Nathanson: Yeah, right. So, there is a lot of different research not just done by me looking and trying to understand sort of recurrence and resistance. So, this is true generally in cancer, particularly when we treat patients with targeted therapy, we want to understand why cancer is recur or resistant to therapy. There are some sort of general paradigms around that and so many times when you look at resistance to therapy the mutation that causes resistance – and this is true again – happens in the same gene in which the mutation is associated with the disease or the disease susceptibility. So even what we call somatic so for example, things like BRAF which is associated with melanoma, the resistance to some of those drugs happen again and BRCA1 and 2 probably the best or most well elucidated variants are what we call reversion mutations. So, the idea is that you actually take a BRCA1 and 2 mutant cancer, something called a parp inhibitor which helps to work together…with oss of function. So let me just take a digression here.

So BRCA1 and 2 is associated with homologous recombination deficiency and when you have deficiency and the cancer is in…you lose function of homologous recombination, the cancer has become dependent on other forms of DNA damage repair. And so, what they come out as they come in, the drugs come in and they hit those forms of DNA damage repair. So, you have multiple sorts of hits affecting the cancer and causing regression because they can't repair their DNA and they can't go, and you treat the cancer by doing that.

So, what happens then is that the cancer is, I mean, I say they're smart, but I don't know if that's anthropomorphizing the cancer is not really where we're going here. But nonetheless what they do is they try to sort of reintroduce the function of the BRCA genes because that's again where it's targeted. So those are called reversion mutations. And so those mutations go in and they sort of come in and they basically helped to take out the mutant piece of DNA and where the mutation is usually right around where the mutation is that you sort of chop that part out and then it reports sometimes with partial functionality but functionality of the Gene and so that's called a reversion mutation. So that's one of the more well-known and well documented mechanisms of resistance.

Our studies actually we went to look at sort of beyond in reversion mutations at the parp Inhibitors and sometimes with other kinds of DNA damaging agents. We want to look but many people get treated with

standard of care therapy rather than just with parp Inhibitors. And so we went to look at some of the reversion mechanisms there. So, we identified sort of three possible reversion mutations and one of the things that I think we had actually originally well-documented, it was one of these things where we put some out some paper and a data and people are like, oh no, but like I have to say I've never been told I was brave to publish something before but it was that was the data and it's been subsequently validated in a lot of other studies.

But essentially, as I mentioned like in the tumors you lose both the genes but that's called loss of heterozygosity. But sometimes you see tumors where only one of the gene is lost, so the mutant alleles there and then the tumor, the other wild-type layer is there and what we had shown previously was that those tumors are actually resistant to many of the DNA damaging therapies, not surprisingly. So if loss of heterozygosity or violating an accusation is not present – those tumors actually don't respond to the agents that are developed to target it, not surprisingly. But that hadn't been as sort- of well recognized — in that — first of all there are percentage of tumors in patients with germline BRCA1 and 2 mutations that didn't have loss of heterozygosity and didn't respond. So, what we found is that some of the tumors go back and forth between this state of loss of heterozygosity and non-loss of heterozygosity in a way to develop resistance actually and that was relatively new.

We also found that there are actually different splice variants. So, all of the genes in the genome, they're not just have one version coming out of mRNA, there's multiple different versions of the mRNA. And so, we found that resistance favored certain versions of the RNA which probably are more stable and more likely to go to make more of the BRCA1 and 2 especially BRCA2 Gene and BRCA2 protein.

And then we also found that not surprisingly again, you're looking where you're treating is where you see resistance, right? So, the other thing is we found that some of the tumors had very high level of the parp one protein which is targeted by parp Inhibitors and those tumors tended to also be more likely to be resistant. So, there are sort of different mechanisms on the protein, the MRNA and different DNA levels all of which are sort of in the same pathway, sort of trying to counteract resistance. Again, I think it's nice because although there are new mechanisms of resistance, they sort of all falls within the same pathway to be able to identify them, right. I went on a while there.

Shweta Mishra: No. Thank you for distilling such complex information for us doctor. So, before I jump on to invite Heidi in the conversation could you please touch upon a bit on the treatment modalities? What does all of this mean in terms of of developing new treatments?

Dr. Katherine Nathanson: Right. So, I think one of the big focus now is not on treatment but on cancer interception, so that's something where the Basser Center for BRCA, which is a 10 and really an amazing place to work and a lot of investigators focused on work on BRCA1 and 2. The big focus now is in on an interception. So, what is interception? Interception is the idea that you can sort of stop a cancer before it starts and there's all sorts of analogies. The one that people talk about is weeding the garden like taking out the bad cells before they have a chance to develop into cancer. And so, a lot of the focus is trying to understand whether or not there are different therapies that could potentially help there. So, one of them that's being tried for example or trying to understand is could one give lower doses of parp inhibitors for long to treat people to try and reduce the cells. Dr. Susan Domchek who leads the Basser Center is doing a vaccine trial to see if there is a way to vaccinate healthy individuals to try to target some of the cells that may be abnormal. But, you're still again trying to use the immune system to take get rid of early cancers or early cancer cells. So our work on LOH has really shown the importance that you have to lose both alleles and that you treat tumors differently depending on what their molecular features are at the beginning and now we're sort of going back and back to see what's happening in the normal tissues and what's happening in the pre-cancer to try to understand how we can move that onto interception therapy and that's really the next step in what we're doing.

Shweta Mishra: Right. Interesting, that sounds hopeful and thanks for sharing all of that and with that I will now invite Heidi to the discussion. Heidi, please take it away.

Heidi Floyd: Hello. Thank you. Thank you, Doctor, very much for your help. I have a couple of questions. Just based on what you said. If you don't mind they're kind of off script, but I really am curious to know first when you talked about the founders, the people that have really high percentage of BRCA1 and 2 and you mentioned one specific group, what are the names of other specific groups that are in that same like the Ashkenazi Jewish people who else would might…

Dr. Katherine Nathanson: So, there is actually that French-Canadian founder, for example, Pakistanis have those particular founders. There are some Eastern European founder mutations. So again, these are doesn't matter what ethnic group you are, you can have a BRCA mutations. And again, this is a phenomenon we're discussing in the context of BRCA1 and BRCA2 that this happens with any kind of genetic diseases.

Heidi Floyd: That's it. That was kind of my point that it's not just focused in one particular area its global, right? It couldn't be….

Dr. Katherine Nathanson: We have one that I deal with, I do something called VHL which is called Chuvash polycythemia, that's a Founder on like one Island.

Heidi Floyd: Wow cool, not cool but still you know what I mean still fascinating.

Dr. Katherine Nathanson: Yes.

Heidi Floyd: Very good. Thank you. And you were talking about using like healthy tissue healthy women with healthy …. There's a healthy breast tissue bank at the University of Indiana. I think are you familiar with that.

Dr. Katherine Nathanson: Yeah, the Komen Foundation.

Heidi Floyd: Okay. Yes.

Dr. Katherine Nathanson: We are actually focused very much on… We collect a lot of healthy breasts from BRCA! And 2 mutation carriers at the Basser center because we're interested and we work with them and with a great foundation on doing this called a pre-cancer atlas and the idea is to really try to understand sort of what's happening as I said before cancer starts, so that we can intercept changes and that's a collaborative effort across several institutions.

Heidi Floyd: I love that, and I think first of all for someone like myself who's a breast cancer patient and a fierce advocate like to me that just represents hope. What you just said is like a glowing beacon for the future that we can all kind of march to. So, I'm really really happy with that. So, going into my questions that I have kind of prepared for you. What advice would you give to young women who are faced with this genetic predisposition for other ovarian or breast and other than the standard of eat right and exercise, what are your thoughts about things like preventative mastectomy or Oophorectomy both of which can have long ranging effects, lasting the rest of their lives?

Dr. Katherine Nathanson: I think its a great question and a really complicated question. So, I think first of all its important to recognise we're talking about BRCA1 and 2 as sort of a high-risk breast and ovarian cancer genes in which mutations…. But there are a number of other genes in which you see risk. So, we call them sort of I would put PALB2 and sort of high to moderate and then moderate penetrance gene sort of CHEK2 and ATM and so the answer is really varying depending on which mutation a patient has. So, I just want to say like it's not one size fits all when you ask those questions about risk. There are other genes that are rare and RAD51C, RAD51D and things like that. So, what I say to people is I think that it's really important to understand the risk. I think it's really important to talk to people who do this and are experienced in doing this and have done this, seen many patients, really understand the risk. Risk is incredibly hard concept for people and I think that that's something that is really having someone who's well-informed. I think the

individual decisions about things like mastectomy and Oophorectomy, those are decisions that are made in concert with your physician. There's no one right choice for any one person. So, I think that it's really important to have those decisions. I can say that for breast cancer sort of the universal guidelines suggest that screening is good. We have good screening for breast cancer. We have MRIs, we have that and so that's a discussion that is had with people. For ovarian cancer screening is not as good and so I think the recommendations really are for prophylactic oophorectomy for high-risk again for BRCA1 and 2 and those recommendations so the age varies based on BRCA1 versus BRCA2 slightly later for BRCA2 and there's also some trials that people might be interested in, for example, WISP trial where they do prophylactic removal of the Fallopian tubes for people because we know very uncommon cancer comes from the Fallopian tubes and that might do a variant cancer removal. Some people may have when they have their tubes tied, have their Fallopian tubes removed for example, and then go later onto prophylactic oophorectomy. So, I think again, there's sort of a lot of different options that really should be decided on concert with physicians.

Heidi Floyd: Excellent. Thank you. Can you talk a little bit more about the PALB2 that you just mentioned because we have to tell. So, tell me I guess just as person, just a Layman, I'm just a breast cancer patient out here talking to a million other breast cancer patients, how can we keep up with everything that you guys are working on? Where is a good repository? What can you do?

Dr. Katherine Nathanson: So, for BRCA1 and 2 on the Basser Center really maintains a very active website where they really put in all the most recent trials, all the most recent information. All of that kind of stuff is really centralized at the bassar.org, which is our website. Really, it's meant to be a one-stop shop for people with BRCA1 and 2 mutations. Obviously Force which not maybe obviously but Force is an organization and a support organization that people use to get information that I think is very important. So PLB2 for those people who aren't as familiar PALB2 is a gene is called Pal of BRCA2 or PALB2 and it's associated with a risk that depends but basically about 30 percent lifetime risk, so lower than BRCA1 and 2. And again when you look at it, you start sort of mammography and breast MRI; Age 30 slightly later than BRCA1 and 2 but still important to screen and then it has a lower risk of ovarian cancer than BRCA1 and 2. So again, that's more of a discussion about prophylactic oophorectomy in that setting. So again, I think it's really important to have these discussions in the context with your physician and their individual decisions.

Heidi Floyd: Very good. Thank you. Some people just like myself. We have breast or ovarian cancer and a long long family history of that but when we go to be tested for any of the BRCA, anything, it turns out that we test negative, for any of the mutations. Now how frequently should we go back and retest if we're concerned about things like generational, you know what I mean if we have children?

Dr. Katherine Nathanson: I think it's a really interesting question. So, my first answer is you should participate in research that's really important. We're not stop looking at genes that are associated with breast cancer. One of my current projects for example is to look at sort of the non-coding regions around BRCA1 and 2 maybe there are variants there that we currently don't test to for in that are associated with genes. So, really important to participate in research. We're not, we haven't forgotten about you that you are negative. We are actively, that's what we're actively working at actually. Like sure I work on BRCA1 and 2, we work on modifiers, and we work on all sorts of stuff like that. But we also really actively work on who is negative, that most women are negative. I just want to point that out when you get testing most women are negative and we really want to find answers for those women. That's really still really important part of our research. I do research funded by the Breast Cancer Research Foundation, by CureBRCA, all of these people lot of that's focused on trying to find either new genes or new variants in the genes that we have. In terms of retesting, I think that's a really interesting question, but I would say like that's a knowledge thing right now like the genes that we do testing for breast cancer actually has remained fairly stable for the last least five years I would say. So, like people who have been tested, if you are only tested for BRCA1 and 2 absolutely go back and you need to be retested. But if you were tested for BRCA1 and 2, ATM, CHEK2, PALB2 and RAD51C, RAD51Dyou're pretty much done and there's not new genes right now. I'm not saying there won't be new genes, I'm not saying there won't be new variance, but we've been pretty stable for a while. And so, I think it's going to take a lot to sort of change that sort of stability but I do agree like how

do you know there are new genes and people are testing for how do yo know there are new valid genes? I mean, I think one of the things I've been doing this I'm old, I've been doing this for a long time so genes come and go and so I think it's one of the things that I really like to do is like make sure something sort of stable. And there are genes that have been removed, we used to do NBN testing. It's been shown as really not associated with an increased risk. It's off, it's not on all the panels anymore, right. I can name other genes that sort of the most obvious one. And so, I think that you sort of want to get to a period of stability where things have been done and gone long time. And for you someone is a survivor, it's slightly different. I think the big issue is for someone who's not unaffected and how you do screening. So, there are lots and lots of models for breast cancer risk, so Tyrer–Cuzick, BOADICEA, Gail all sorts of different models. So, it's important for someone with a family history or some concern to have an evaluation and go through a model. If you have a more than 20 percent lifetime risk than MRI would probably be recommended. So, you need to sort of have that go through the testing and have evaluation that's slightly different than someone who's had breast cancer, but if you have a strong family history, and you have for example and I'm making this up, I don't know anything about her history just as an example that hasn't had cancer, sort of have that sister has her sort of modeling done turns out what her lifetime risk is to be able to go for screening is important to do.

Heidi Floyd: Thank you and so why there are two really important things that I think I picked up on what you just said I'm really grateful. First if you are a breast cancer survivor you are still needed in things like clinical trials research.

Dr. Katherine Nathanson: Absolutely. I realised I should have said, I should say if you're a breast cancer survivor is they just changed the guidelines about genetic testing, I don't know people have been it's not been really well publicized but it's new guidelines for ASCO just came out last month that suggest all women with breast cancer under 65 should get genetic testing. And the NCCN guidelines are likely to follow the ASCO guidelines. And so that's actually just changed. It's not the genes have changed, who gets testing? Have changed actually and so I think that that opens up testing for a lot of people who are survivors. Actually, that's all-important point. I realize I digressed, but I just wanted you to know.

Heidi Floyd: No, that's good.

Dr. Katherine Nathanson: And it's actually interesting we were just talking about it like it on an email chain on a bit hasn't got a lot of publicity which is kind of surprising to us. You would have thought it would have been sort of pick up but that was recently published in JCM.

Heidi Floyd: Well, I will put it out in the Cancer Community my friend. I'm pretty sure we can…

Dr. Katherine Nathanson: It's recently been there and it really wasn't like, Mark Robson I think was the senior author on the ASCO guidelines. Its been surprising no lot of discussion about that. I think it ends up a lot of discussion who is into the testing, another discussion, and another about that. But yeah, I mean, I think there are oh my gosh I have totally lost my train of thought where we are going.

Heidi Floyd: Where if we are breast cancer patients and we do want to help participate in things like that. We just go to your website for like clinical trial information, how we can jump in? Okay.

Dr. Katherine Nathanson: Yeah, and so yes, and we're always collecting, so basser.org is a great website and we are always collecting people who are at high risk for research. That's something we're very interested in. Yeah.

Heidi Floyd: Okay and for my fellow patient if you have been diagnosed more than five or six years ago, consider getting retested because they have….

Dr. Katherine Nathanson: Yeah, you know 5 or 6 years ago they were doing the testing for those genes, it just depends on the lab, and it depends on who got tested but the retesting is like if you just had BRCA1 and

2 which is sort of where people yeah, you need to be retested. But if you had all those other genes, no not at this point.

Heidi Floyd: Okay, excellent. Well, thank you very much. I really appreciate this has been fantastic.

Dr. Katherine Nathanson: No problem. Happy to help. Happy to do it any time.

Shweta Mishra: Thank you, Heidi. Thank you, Dr. Nathanson. Quite an insightful conversation but let us try to wrap up the show today. Dr. Nathanson, thank you for sharing your expertise with us on this very informative session. Heidi, thanks for guiding the panel with your insights. We also thank the University of Pennsylvania, and we will make this talk available on curetalks.com soon. So, until next time, thank you everyone and have a great day.

Thank you.