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Cancer Conversations

Episode 2: The Truth About BRCA Testing and Genetic Risk

Announcer: Welcome to Cancer Conversations, a podcast series from Dana-Farber Cancer Institute. In this Episode from July 2014, Dr. Huma Rana, Clinical Director of Dana-Farber's Center for Cancer Genetics and Prevention, gives an overview of the link between genetics and women's cancers, and why some women have a higher risk for developing disease. Anne Doerr from Dana-Farber's communications department joins her for the conversation.

Anne Doerr: Let's start today by hearing a little bit about you, Dr. Rana. How did you get into this field?

Dr. Rana: As you know, I'm Clinical Director of the Cancer Genetics and Prevention Disease Center. I'm trained in internal medicine and in genetics, and I focus only on hereditary cancer predisposition syndromes.

Anne Doerr: Terrific. OK, we'll start with the questions then. Right off the bat: Who should seek genetic testing?

Dr. Rana: That's a great question. There are various criteria for having genetic testing or seeking genetic testing. In general, obviously, if there's a mutation present in someone's family, the family members should undergo genetic testing specifically for that mutation or alteration. There are patterns of cancers that can suggest that there is an underlying mutation present in a family. Some of the things that we look at are families where there are multiple people with breast cancers, premenopausal breast cancers, or breast cancers diagnosed under the age of 50.
This is per the new NCCN guidelines:

- As of 2014, anyone diagnosed with an ovarian cancer should have genetic testing, a primary peritoneal cancer, or a fallopian tube cancer. It's essentially the same type of cancer, so they should have genetic testing.
- People who have cancers that develop at much younger ages of onset than would be expected—young colorectal cancers.
- People who have had more than one type of cancer—someone who has had separate breast cancers or bilateral breast cancers.

As you can see, the list is pretty long, and it's ever expanding. People who have had pediatric cancers are also at risk for harboring a hereditary predisposition.

Anne Doerr: You know, and for some people, it might be a little scary when they think of genetic testing, but what is the process like? What does it entail?

Dr. Rana: It involves meeting with a genetic counselor, reviewing one's personal and family history of cancer, talking about the risks and benefits of genetic testing, going over the implications of genetic testing (either a positive test result or a negative genetic test result), and essentially, signing some papers and having one's blood drawn or having one's saliva tested.

Anne Doerr: Nothing too invasive?

Dr. Rana: Nothing too invasive.

Anne Doerr: OK, great. What kind of information should someone provide to a genetic counselor?

Dr. Rana: If someone has had cancer themselves, bringing their pathology report is incredibly helpful. If they haven't had cancer and there's a strong family history of cancer, they should know the ages at diagnosis of cancer in their family members and the type of cancer that was diagnosed. If they have pathology reports of their family members, that can be very helpful, because sometimes the specific histology on the pathology report of a cancer can be a clue to an underlying mutation. If family members have had genetic testing, bringing those genetic test results or copies of those results (whether they're positive or negative) can be helpful, because then we can look at the type of testing that's been done, or the extent of testing that's been done previously in the family. Information about premalignant conditions, like DCIS or colorectal polyps or adenomas, is actually very helpful.

Anne Doerr: OK. We touched upon this a little bit with family history, but what's the difference between inherited genetic mutations and nonhereditary gene mutations?

Dr. Rana: Essentially, all of the cells in our bodies, all of the cells that make up our tissues and organs, every cell, except for red blood cells contains our genetic information, and that includes 22,000 genes. Cancer cells or tumor cells use the same genes that we have in every cell of our bodies. They exploit those same genetic pathways. They grow by causing mutations or causing tumor-suppressor genes to not function, or by enhancing the function of genes that help them to grow (called oncogenes).

When we talk about hereditary genes, we're talking about the ones that we're born with and that we pass down that are present in all of our cells. When we talk about ones that are not hereditary, we're often talking about alterations that are present within the tumor or within the cancer.

Anne Doerr: One viewer asked: For hereditary breast cancer risk, which family member's cancer history matters most?

Dr. Rana: That's an interesting question. I think that sometimes we hear people say that the mother's family matters more. That's actually not true. Half of our genetic information is inherited from our mothers; the other half comes from our fathers. So, if there's a striking family history of breast cancer or ovarian cancer on the father's side of the family, that's just as important, just as salient as the mother's family history.

Anne Doerr: Another question is: I was tested for the BRCA 1 and BRCA 2, and the results were negative, but I was still diagnosed with breast cancer—why is that?

Dr. Rana: Breast cancer is a multifactorial disease, meaning that the development of breast cancer is due to a number of things that can occur. It can be genetic. It can be environmental. It can be lifestyle related or hormone related. So, testing negative for BRCA 1 or 2 doesn't mean that someone won't develop breast cancer. We know that BRCA 1 and 2 are really just a small portion of why people develop breast cancer in terms of any [inaudible 00:06:32] with breast cancer or families with breast cancers. Those genes only account for 5% to 10% of the breasts cancers that occur.

Anne Doerr: OK, there are a couple of parts to this one, and you kind of touched on them a little bit. This viewer says: How does a person acquire the BRCA gene when there is no family history? Is it spontaneous? She says she is BRCA 2 positive, and she does not have a family history of the gene. Although her mother died last year at the age of 97, she had breast cancer in her 70s.

Dr. Rana: For some genes, there is something that we call a de novo mutation rate. Most genes have that. That means that when the egg and the sperm come together, there's a new mutation that occurs. For the most part, BRCA 1 and 2 mutations are inherited, so one would expect that her BRCA 2 mutation is either from her mother or from her father.

What we often can see is that these are inherited from the fathers. If there are not a lot of women on that side of the family, it can appear as though there is no hereditary breast cancer, but the truth is that that side of the family is just not informed of their mutations.

Anne Doerr: Right. Another question from a viewer… She says: I have tested positive for the BRCA 2 gene mutation and was diagnosed with Stage III breast cancer in August 2010. Three years later, I found out that the cancer had metastasized to my liver and bones, and I was diagnosed with thyroid cancer. Is the thyroid cancer due to the BRCA gene?

Dr. Rana: Not that we know of at this time. I think that, thus far, no studies have shown that having a BRCA alteration causes a higher risk of thyroid cancer, but I think as more and more people are tested, it's possible that new associations may emerge.

Anne Doerr: We just don't know yet.

Dr. Rana: Exactly.

Anne Doerr: This viewer says: If my mother was positive for BRCA, and I am as well, what are the chances my daughter will test positive?

Dr. Rana: For someone who has a BRCA mutation, that means they have one working copy of the gene and one non-working copy of the gene. When you have a child, it's by chance which copy is passed down, so it's a 50/50 chance for any first-degree relative of someone who has a mutation. That's daughters, sons, siblings, all of them.

Anne Doerr: And at what age would you recommend children undergo genetic testing if you had questions?

That's a good question, and it really depends on the cancer syndrome. For BRCA 1 and 2 and for things like Lynch syndrome, the risks are mainly adulthood cancer risks, so we recommend people wait until they're at least age 18, or at the time that their cancer surveillance or risk management would change. For BRCA 1 and 2, that's at about age 25. There are other cancer syndromes—Li-Fraumeni syndrome, familial adenomatous polyposis, MEN2 (multiple endocrine neoplasia type 2), where there are pediatric cancer risks… In those situations, we do recommend that children be tested.

Any question like that would be something you discuss with your doctor.

Dr. Rana: Exactly.

Anne Doerr: This viewer says: My maternal grandmother, aunt, and cousin—all on the same side of the family—have been diagnosed with breast cancer. My cousin has been tested for the BRCA mutation, but it came back negative. I see an oncologist on a regular basis due to the family history of cancer, but would you recommend genetic testing as well?

Dr. Rana: It sounds like this person is getting the care that she needs and close surveillance by an oncologist. There is a concern on that side of the family with the grandmother, the aunt, and I imagine it's that aunt's daughter that has breast cancer, and it sounds like that cousin has tested negative for BRCA 1 and 2, but I think that there's updated genetic testing that that cousin who is affected could do, and that would probably be the most informative for everyone. BRCA testing has changed so that it's more comprehensive. There are now other genes that can be evaluated. The next best step is having the affected individual in that family, the cousin, have more testing.

Anne Doerr: This person says: Is it OK for someone with a positive BRCA mutation to take birth control pills, and do they have any correlation?

Dr. Rana: That's a question we get a lot. There is some data to suggest that women who take oral contraceptives, including women who are at high risk for breast and ovarian cancer, can reduce their risk of developing ovarian cancer by being on oral contraceptives. There has also, however, been data that shows that they may be at increased risk for breast cancer. Those studies have been much more mixed, and they haven't consistently shown that there's a significantly increased risk for breast cancer among BRCA carriers. For that reason, oral contraceptives are not contraindicated in BRCA carriers.

Anne Doerr: OK. This viewer says: I was diagnosed with Stage I breast cancer when I was 38, and the cancer has returned twice. However, I tested negative for BRCA 1 and 2 in 1998. Is it possible there is another gene that may not have been identified when I was tested in 1998?

Dr. Rana: It's certainly possible that there's another gene at play. We know that the testing that was being done in 1998 of the BRCA 1 and 2 genes is nowhere near as comprehensive as it is now. Testing then involved what we call "full sequencing" only—essentially, a spellcheck of the gene. There are other types of mutations or alterations that occur in those genes that are not picked up in a spellcheck or in full sequencing. These missed mutations are called rearrangements or deletions or duplications. Her testing can certainly be updated so that it includes comprehensive testing of BRCA 1 and 2 that includes looking for these other types of changes, as well as screening other genes that are now implicated in breast cancer development.

Anne Doerr: On that question, too: Would you recommend people who had the gene testing done 10 or 15 years ago or longer to come and have it done again?

Dr. Rana: I think that if someone has a striking history, such as this woman who was diagnosed with a breast cancer at age 38, or if there's a striking family history, I would recommend that people be retested. This analysis, this deletion, rearrangement, duplication-type analysis, wasn't instituted until 2006. Even then, it didn't become integrated as part of the test until 2013, so there are probably a number of people out there who have had suboptimal testing of BRCA 1 and 2.

Anne Doerr: This viewer says: My father was diagnosed with prostate cancer in 2006, and I was diagnosed with breast cancer DCIS in 2007. Neither of us has been genetically tested, but is it possible that there is a genetic link between the two cancers. Should I have my children tested?

Dr. Rana: Recently, we've learned that prostate cancers are, in particular, part of BRCA 2, and may also be part of the spectrum of cancers in the BRCA 1. There is certainly evidence that men with BRCA 2 mutations have more aggressive prostate cancers than men without BRCA 2 mutations.
I don't think that this person's children need to be tested, per se. As with most genetic testing, it's most useful if the person who has had the cancer or the precancerous condition undergo the genetic testing.

Anne Doerr: This is an interesting question: In the case of identical twins, do both twins need to be tested if there's a strong family history of breast cancer? I am an identical twin and was told that only one of us needs to be tested to find out if we both have the BRCA gene.

Dr. Rana: That's a good question, and I think it depends on how confident you are that you're actually monozygotic twins versus dizygotic twins. If there's any question at all about it, then I would recommend that each individual be tested. If you're absolutely confident and you've had other genetic testing that shows that you're monozygotic twins, then I think it's less important.

Anne Doerr: This viewer says: I keep reading about genetic testing becoming more common. Are we close to a point where everyone will be routinely screened (if they want) for common genetic mutations?

Dr. Rana: I think we are coming closer to that point, although that point is still probably very far off.

Anne Doerr: Right.

Dr. Rana: The more testing that we're doing, the more changes we're finding in these genes. It's hard to know, from an informatics standpoint, what those changes mean in terms of how they affect the function of the protein, if at all. And then, on an even larger standpoint, it's hard to know what that means for an individual who is carrying an alteration in those genes. I think, ultimately, we will probably get there. We're far from there at this time. Often, the more expansive the testing, more questions that it can raise.

Anne Doerr: This is a big question that a lot of people are wondering: Does insurance typically pay for genetic testing?

Dr. Rana: Most insurance companies have criteria that they've come up with for genetic testing. For some companies, that involves a personal cancer diagnosis. For other companies, it involves that certain family history criteria be met. But most insurance companies address genetic testing in some way.

Anne Doerr: What's the cost if you don't have insurance?

Dr. Rana: The cost is dropping dramatically. It was not long ago that looking at just the BRCA 1 or 2 genes would cost nearly $4,000. As I think many people may know, the Supreme Court unanimously

overturned one company's patent on BRCA 1 and 2, so that led to competition in the field. Basically overnight, the cost dropped by half. Now people can have those genes as well as other genes looked at for out-of-pocket costs that are around $2,000 or less than that. I think that's still a lot of money to spend out of pocket, but I imagine that, with time, it will only go down.

Anne Doerr: Is there criteria for finding a place to get the genetic testing done, as far as finding a reputable place? Should it always be at a hospital? What would you recommend?

Dr. Rana: I would recommend that people have genetic testing done through groups or centers where they have a lot of experience with genetic testing, ideally in a setting of genetic counseling, because I think that a positive test result is pretty straightforward. A negative test result, as we've seen with these questions, can actually be much more complicated. Obviously, when there's any variance or alterations in some of these genes, you just want to make sure that people are looking at the family history and the genetic testing in a rigorous manner.

Anne Doerr: This just in: You mentioned new genes in ovarian cancer development. Can you name them? This viewer says she was tested in 2010 and wondered if she should get tested again.

Dr. Rana: There was a study that was done in 2011 looking at women with ovarian cancer. They looked at a number of genes that are associated with cancer development. Some of them are genes that cause colorectal cancer and endometrial cancer, and some of them are genes that are within the BRCA 1 and 2 pathway, meaning that the proteins that those genes produce work closely with BRCA 1 and 2 to repair errors that occur in DNA. Some of those genes are called PALB2, RAD51C, and RAD51D. There is more testing that is available to people, and she could certainly have more expanded testing.

Anne Doerr: Another question for someone who just sent this in: I am trying to decide whether to have genetic testing for the BRCA gene. I was treated for AML Leukemia in 2012. I had chemo and stem cell transplants. I was just diagnosed with stage 0 grade 3 breast cancer. No one in my family has had genetic testing. I have a daughter and two sons, and I am concerned about their cancer risk. She's trying to decide if she should get genetic testing.

Dr. Rana: I think that, given her history, I would probably think about some other genes in addition to BRCA 1 and 2. She has had a stem cell transplant, so her genetic testing would need to be done, essentially, on a skin biopsy. If she were being seen here (or wherever she were being seen), they would do a skin biopsy. They would culture the cells from the skin biopsy. Essentially, they would culture the fibroblast. They would isolate the DNA from those fibroblasts, then send that for genetic testing, because obviously the blood testing would not be her DNA.

Anne Doerr: Right. Can you offer some prevention tips for women who have tested positive for BRCA mutations?

Dr. Rana: We know that women with BRCA mutations have a 50% to 85% risk of breast cancer over their lifetime compared to the general population risk of 10% to 12%. There are a number of management strategies. Some of them are surveillance, and it sounds like this person is asking specifically about prevention. When it comes to preventing… And was it breast cancer or any cancer?

Anne Doerr: Breast cancer.

Dr. Rana: OK. So, when it comes to preventing breast cancer in BRCA carriers, there are a few strategies. One is called "chemoprevention." Medications like tamoxifen, raloxifene, exemestane have been shown to reduce the risk for invasive estrogen receptor- or hormone receptor-positive breast cancers. That's one option that's available to people. Another option is bilateral preventive mastectomies, which reduce the risk for breast cancer by about 90%--very effective prevention.

Anne Doerr: Someone just wrote this in: Would you recommend pelvic exams and pap tests for someone who is BRCA 1 positive but has had ovarian and fallopian tubes removed?

Dr. Rana: Pelvic exams are actually now controversial, and the recommendation for pap smears has also changed recently. I would recommend that the person have regular gynecological care with her physicians. Those tests are mainly targeted for other cancers, not for BRCA-related cancers. Paps were developed to find cervical cancers.

Anne Doerr: And finally: Is there any new or upcoming research that you would like to share with regards to genetic testing, something that may make a difference in the lives of patients?

Dr. Rana: I think that one of the things that's new and exciting and is going to make a difference for patients are these other genes that we're finding in families. There have always been families that have increased risk for breast cancer and ovarian cancer, or just breast cancer, or just ovarian cancer. Thus far, testing has been negative in those families.

We are starting to find changes in other genes that could explain those families, and I think that that's the most exciting thing at this time. It took 20 years or so for us to get to where we are with BRCA 1 and 2. It will take some time for us to give that information back to people and say, "A mutation in the PALB2 gene means that one's risk for breast cancer is X," or "Their risk for ovarian cancer is increased or not increased at all," and that's what a lot of the research is focusing on now.

Announcer: This has been Dana-Farber's Cancer Conversations featuring Dr. Huma Rana of Dana-Farber Center for Cancer Genetics and Prevention. To download more episodes and learn about other cancer podcast series, visit Dana-Farber.org/podcasts.