Approaches to Prevent Breast Cancer Recurrence

Breast cancer recurrence, often occurring years after initial treatment, poses a significant challenge to patients and caregivers. Dormant tumor cells, also known as ‘sleeper cells,’ persist in the body after treatment and may reactivate to cause recurrence.

Predicting recurrence remains elusive, leaving indefinite treatment as the only option for relapsed patients. However, recent research suggests a promising approach – that is – targeting dormant tumor cells before they can trigger recurrence.

We are talking to Dr. Angela DeMichele of the University of Pennsylvania to understand in depth about why breast cancers recur and learn about approaches being investigated to prevent relapse. Dr. DeMichele is leading a project to develop targeted therapies to prevent recurrence.

Full Transcript:

Shweta Mishra: Hello and welcome to CureTalks. I am Shweta Mishra, and today we are talking to Dr. Angela DeMichele of the University of Pennsylvania to understand all about breast cancer recurrence and gain insights into the novel approaches being investigated to prevent relapse. Dr. DeMichele is Alan and Jill Miller Professor in breast cancer excellence and in addition to several key roles she is the co-leader of the breast cancer research program and co-director of the 2-PREVENT Breast Cancer Translational Center of Excellence at the University of Pennsylvania. Joining Dr. DeMichele on the panel is Heidi Floyd who is a sought-after influencer with several years of experience in healthcare advocacy and breast cancer nonprofit management and is also an international speaker and a published author. Welcome to CureTalks Heidi and Dr. DeMichele, it’s an honour to have you here on the panel today.

Dr. Angela DeMichele: Thank you.

Heidi Floyd: Thank you. So good to be here.

Shweta Mishra: Thank you. Dr. DeMichele you specialize in pioneering therapies for breast cancer, and you are leading projects to develop targeted therapies to prevent recurrence. But before we dive deeper into the subject, I think it would be great to start by touching upon the basics of why do breast cancers relapse and what types are more prone to relapse?

Dr. Angela DeMichele: So, thanks for that question. So, when we typically think about breast cancer we often talk about the fact that we now diagnosing at earlier and earlier particularly through mammograms and that’s because we know that breast cancer starts in the breast and when it is found early in the breast it is a

very curable malignancy. But we know that up to a third of women who have breast cancer diagnosed within the breast will later develop a recurrence of the breast cancer somewhere else in the body, we call that metastatic breast cancer. And that is typically found in the bones or the lungs or the liver. And that is the real problem with breast cancer is when it becomes metastatic. So, when we wanted to make this link between early breast cancer that's in the breast and metastatic breast cancer, for many years we didn't know how that happened. We knew that we would find the lump in the breast and do surgery, radiation, chemotherapy, often adding anti-hormone therapies, and we would think that everything was fine, and the patient was cured and usually the follow-up to that would be watchful waiting and just looking for symptoms.

But we knew that there was this risk, we would try to predict the risk and it wasn't a very precise science. In the last 5 to 10 years, we've learned much much more about what happens between the development of that primary breast cancer in the breast and the development of metastatic disease, and we now know that there are specialized cells within the breast tumor that are able to escape from the breast and travel either within lymphatics or the bloodstream and these cells can travel to distant sites. But we also know that there is a latency period meaning that the cells don't go there immediately, and this is why many women don't relapse for months to years or even decades after their initial diagnosis. These cells can remain in the system, and they can enter a phase called dormancy where they are essentially sleeping, and these cells can remain asleep for quite some time before reactivating and then traveling to distant sites. So, it was really the biological unraveling of this entire process that now makes it possible for us to start to look for these cells in patients who've had breast cancer and then more importantly if we find the cells to try to do something about it to prevent the cancers from spreading and coming back someplace else in the body.

Shweta Mishra: Yeah, thank you for touching upon the dormant cells. My next question was about them. So, it just feels so curious to know about what is so special about these cells? Why are they so resistant to cancer treatments and how are the different from a normal cell or a cancer cell, right? And if you could touch upon, how do you see them being useful in developing therapies to prevent recurrence?

Dr. Angela DeMichele: Those are great great questions. And I think we're just at the beginning of really fully understanding biologically what these cells are, what we know so far is that these cells are able to break through the boundaries of the breast they're able to stay alive in the circulation and then they go into this dormant or sleeping state once they reach a tissue that's welcoming to them and often that is the bone marrow. So, the bone marrow is a location where these cells can burrow in and then they stop dividing and I think about this a lot like a bear hibernating in the winter that it goes into a cave and goes to sleep, it doesn't need any outside energy, food, water etc. But then spring comes along, the bear wakes up and emerges from the cave and it's very similar with these dormant cells, they stop dividing. They don't need external energy sources, they're able to stay alive, even though they're not dividing. And that is really the key identifying feature of these cells but it's also the key to understanding how to treat them because all of our treatments for cancer have been developed to attack dividing cells.

That's what cancer is, cells that are dividing out of control, right? That's how we typically thought about what cancer is. So, this now introduces a new kind of cancer cell, a cell that's quite quiescent, a cell that's not dividing, a cell that's not really using all of the typical signals but is also remaining invisible to the immune system. And that's another key feature is that these cells are hiding there in plain sight and the immune system can't see them. So, what we're trying to understand is what are the key things that we can attack in these cells that are allowing them to stay alive and how can we make them visible to the immune system?

And those 2 things I think really then open the door to treatment. So, for example, we have learned that the cells use a process called autophagy to give themselves energy. That means that they can actually consume their own internal proteins as an energy source. We need to use drugs that interfere with that process, to kill these cells then we can starve them. But unless we knew that we wouldn't know what to be targeting. In addition, we're starting to see how the cells hide themselves from the immune system and I like to think about this like the Harry Potter invisibility cloak, the cells have these proteins on the surface that really make them invisible, and we now have ways in which we can remove that invisibility cloak and make them visible

to the immune system so it can attack them. So, these are just a couple of examples of ways in which we now can understand what the targets are so that we can develop therapies that can eliminate the cells. And I think this is important because there's a fixed pool of these cells in the body. If we could eliminate all of these cells, then we would not have any patients develop a recurrence. No patient would get metastatic breast cancer, if they started with an early-stage cancer. That would really close that gap in curing that last 20 to 30% of women who still die of breast cancer. So, this really would make an enormous difference in survival from breast cancer.

Shweta Mishra: Right. Thank you. Thank you for explaining this in such an interesting way and I really like the analogy of the invisibility cloak that you mentioned. Thank you for that. So, are there some other approaches being studied to prevent recurrence that have high chances of developing into therapies apart from dormant cells treatment?

Dr. Angela DeMichele: There are. So, there are many ways that we can think about trying to do this all along the pathway for these cells to develop, survive and travel. And one thing that also has been developed in the last few years is the idea of finding the cells while they're traveling through the bloodstream. We now have a really sensitive technique called Circulating Tumor DNA, CT DNA that many of you may know have heard about. This refers to the fact that when cancer cells are present in the body, they shed parts of their DNA And this DNA is floating around in the bloodstream. And so, we can now detect it with super sensitive methods. So, if you knew that there were cells floating in the bloodstream for example, you could also target those cells and we believe that those cells typically are still dividing. So those cells need a different approach.

So, if we step back and look at the entire process, we now know we need to treat the cancer that we find in the breast and the lymph nodes around the breast. We likely need to clear any cells that are floating around in the bloodstream. And then we also have to eliminate that pool of dormant cells that are just lying in weight. And so, it really needs to be a comprehensive approach that looks at each of these different areas and targets them in very specific ways. We do a wonderful job of eliminating the cancer in the breast and lymph nodes. And now it's the bloodstream and the dormant cells that are really our target.

Shweta Mishra: Right. Thank you. We look forward to following all these developments on that front doctor and I just have one more question before I hand it over to Heidi. So, Doctor recurrence is one of the big big reasons why people decide to get their breast tissues removed all together. And it's not an easy decision to make and I know a good number of folks who would not want to do that. So how can a breast cancer patient lower their risk of recurrence apart from getting their issues removed?

Dr. Angela DeMichele: Well, I think that's a wonderful question and I often worry that patients are a bit confused about this because as I was just talking about it is those cells that are in the bloodstream, bone marrow hiding out in various places. Those are the dangerous cells and so removing the breast does not eliminate those cells, what removing the breast does is prevent new breast cells from turning into breast cancer. So, it's extremely effective in preventing new breast cancer and it is a very good and important strategy in women at very high risk of breast cancer like those who have BRCA mutations. But for a woman who has already had breast cancer, removing the breast themselves does not eliminate the problem. So, we have to make sure that we're clear about not doing surgery for a solution, that isn't the right solution to the problem.

Shweta Mishra: Okay, so, any lifestyle advice that you would like to provide to the patients to reduce their risk?

Dr. Angela DeMichele: Well, there are a number of lifestyle alterations that have been shown to reduce the risk of recurrence. I do think that these have an impact, although it's not as strong an impact as we would like to see. So, exercise has been found to be productive and that's typically recommended to be 30 minutes of exercise 5 days a week. We don't know exactly why exercise does this, but it could be that it releases endorphins and other hormones that have an anti-cancer effect. It's also been shown that alcohol

consumption can also increase the risk of recurrence at least in laboratory animals and in some of the epidemiologic studies that have been done. And so, we do recommend that women really cut back on their alcohol use. It isn't clear if there's any amount of alcohol that is safe for women who've had breast cancer. So, we really try to ask women to go down to as little as they possibly can.

We also think a lot about diet, and I really wish that we knew how to prescribe a diet that could prevent breast cancer recurrence. So far, we don't really know what things in the diet promote recurrence and what things in the diet protect against recurrence. We do think that Hormones in in our food supply could have something to do with this. And so, we would like to eliminate dairy, meat products where there is hormone use. It could be that antibiotics in our food supply have something to do with it. But the data here is very very lacking. We need more information about diet in order to know what we can prescribe that would be truly beneficial. There is not strong evidence right now that any specific diet is protective. There's not strong evidence that for example a micro biotic or a macrobiotic or a ketotic diet are useful and I know there are many patients who want to feel like they can do something. And I just worry that some of these more restrictive or expensive diets might not be helping. So, we need more research in this area.

Shweta Mishra: Absolutely. Thank you for sharing that, Doctor. I guess with that I now invite Heidi to the discussion. Heidi, please take over.

Heidi Floyd: Thank you so much. Hi, Dr. DeMichele. I really appreciate what you've said so far. It's really been informative for me as a cancer patient but also as an advocate so I could take this information and like spread it out amongst the community. And speaking of the community, I think it's really delightful that you refer to the Harry Potter cloak of invisibility. One of the things in our cancer community if we are talking to someone who doesn't know anything about cancer or doesn't understand what we're going through we call them cancer muggles.

Dr. Angela DeMichele: I love that.

Heidi Floyd: So, it's just an easy little nod don't talk to her, she's a muggle. Oh God. So, my question to you is my first question is and I'm not even going to try to pronounce the drug because I'll do a poor job of it. But I know that you were the key person to give particular new drug to the first patient with breast cancer in a Phase 1 trial many years ago. Can you please talk just a little bit about the importance of the patient enrolling in clinical trials and speak to the best way about how we as patients for our friends or our family, how come we find the trials?

Dr. Angela DeMichele: Yeah, that's such a great question. And first I just want to thank you for all you do for our patients. We work really closely with Patient Advocates. And I just I feel that they're such a critical part of the care team. For every piece of advice, I can give it just has so much more meaning coming from someone who's been through it and for you to give back to other patients that way I think is just so admirable and so appreciated by all of us in the medical community. So, I think the drug you're talking about is IBRANCE or palbociclib. It was a drug that I started studying when it first became available to humans and those drugs IBRANCE, Verzenio, Kisqali, those drugs now have turned into really one of the most important drugs that we use for women who have estrogen receptor positive breast cancer, particularly metastatic estrogen receptor positive breast cancer.

And that wouldn't have been possible without that first patient who volunteered for the clinical trial. She was in her late 30s. She had a young son. She had been through 11 or 12 different therapies at that point, and we were running out of options, and she heard about I told her about this trial I said, I don't know anything about this drug, but it's oral. It doesn't seem like it's going to have a lot of side effects. I don't know if it's going to help you. She said sign me up. I want to do it, I need to do something, and she went on to respond to that drug for almost 2 years and she was looking at very limited time, probably on the order of weeks to months at the time that she entered the trial.

Now this is an extreme example, not every trial is going to have such success for the individual patient, but I

think that what that lesson taught me was that we are partners with our patients and I am so grateful to the thousands of patients that I have come in contact with who have entered the trials. We would not have made the strides that we've made and we're to this day still counting on these support of breast cancer patients in our trials to help us get this last few miles of the marathon taken care of. So, I think that a trial is not for everyone and there are certain times in the cancer journey where a trial is the right thing and other times where standard therapy is the right thing. So, it's important that a patient partner with their provider whether that's their doctor, nurse practitioner to really ask at each stage as they're making treatment decisions, is this a good time for a clinical trial? Should I be considering a clinical trial? Now there are some challenges to finding trials – one of them is that trials are only open at certain places. We would love it if every patient in the country had access to every trial that was close enough to their home for them to participate. That does not exist right now, but that is something we hope we can get to eventually. It's also not free to participate in a trial. And another thing we're fighting is there shouldn't be co-pays for trial participation. We do our best to minimize the cost of participating in a trial.

But the best source of information for the trial is that patient's doctor who can tap into their network to find out where there is a trial in their area, the patient can participate in. There is a website called clinicaltrials.org and that is run by the National Cancer Institute. There are other organizations, like Living Beyond Breast Cancer and the American Cancer Society and others, foundations who can help patients find a clinical trial near them. Here where I practice at University of Pennsylvania, we actually have a navigation program for clinical trials. So, if a patient emails us at breastcancerclinicaltrials@pennmedicine.edu, they will reach us and then we can try to match them to a clinical trial. So, there are more and more of these navigation programs coming around the country that can really help patients navigate this because I think it really is about navigating this network of trials that are out there. And there are so many trials out there and I think many patients don't necessarily know how to get to them. So just ask is the first thing, the other thing that we have is what we call in our ambassador program, which is a network of patients who've been through trials who will talk to patients who are considering trials to tell them what it's about because it can be scary to go on a clinical trial and so nothing like having someone who's been through it to be able to help you understand what it might be about and whether it could be right for you.

Heidi Floyd: Very good. Thank you. I couldn't agree more with you, your statement about the participation not costing the patient more than it already does, right. I mean the financial toxicity that surrounds cancer is something that's rarely discussed but really needs to because we're already paying with our very soul, we shouldn't have to pay with the future of our children going to school or not, I mean, it's huge. So, thank you.

Dr. Angela DeMichele: I could not agree more. It's really a growing group of really committed people fighting this issue because this to me, the finances should not be the thing that keeps a patient from participating in a clinical trial.

Heidi Floyd: I agree and that there I'm going to mention two nonprofits just briefly one is the Breast Fund and that helps pay just normal household bills for women going through breast cancer. And then the other one is the Black Breast Cancer Alliance, and they help people of color find clinical trials and that's kind of my next kind of discussion, in just as an ordinary, average, breast cancer gal who is an advocate I have found that a disproportionately large number of women in color have relapsed reoccurrence, and are also quite hesitant to speak about clinical trials because of history, right? Because of the terrible history surrounding what has happened to people, people of color and women in clinical trial. So, can you speak a little bit about am I mistaken or is it true that people of color have just worse or with large incidents of relapsing reoccurrence and how are you seeing clinical trials with people who are not beige?

Dr. Angela DeMichele: It is a really complicated problem that we have. We need to be able to unravel this issue around whether it has something to do with the biology of race and ethnicity versus access to the best care versus maybe cultural issues around participating in trials or taking certain drugs and I think each of those are contributing to leading to worse outcomes in women of color and we need to attack each of them in slightly different ways, but we have to be aware that all of these issues exist. And so, improving access and building trust and increasing education around what is the best care? where can you go for the best

care? What do these treatments really mean for you? These are things that we are now really building a lot more infrastructure to address because we can't expect to kind of happen without a concerted effort to make it happen. And then there's the biologic issue which is also complicated. We are a melting pot in the United States. There are different biologies associated with different kinds of breast cancer.

So, women of color do not necessarily have more aggressive cancers, sometimes they do sometimes they don't and we want to treat each person as an individual. But again, I think if we can understand whether there are certain patterns, for example, we just did a study in our cooperative group that was focused on this issue of one of our chemotherapies and the problem of neuropathy, which is numbness in your fingers and toes, which can become very debilitating to the point where people can't write, they can't button their shirt, they can't cook and so this is a big problem. And it turns out that drugs are metabolized differently in different ethnic and racial populations and that women black women in particular appeared to have more of this neuropathy than white women who were receiving the same drug at the same doses. And so, we just finished a trial in the ECOG-ACRIN Cooperative Group that looked at the two main versions of this drug and looked at black women in particular which was best tolerated, could we identify the people who are most likely to get neuropathy and how could we figure out whether there was one version of this drug that was better for black women than another.

And these results are going to be presented in June at our national meeting of the American Society of Clinical Oncology. I think they're really, I'm excited. So, stay tuned because I think what's important is we were able to enroll hundreds of women to this clinical trial, black women who typically would not participate but knew we were doing this to help the black community be better treated and the results of this trial are going to help guide how we can really attend to the specific needs of the black community in treating breast cancer. So, I think it's a beautiful illustration of how we can do culturally sensitive clinical trials to really approach these very specific problems in certain ethnic and racial minoritized groups.

Heidi Floyd: Thank you. I'm glad you mentioned the ASCO event. My big fat dream is that ASCO one day will open with a cancer survivor as the keynote. Like that's it, just to celebrate what the end result is, right? So that's just between you and me. So, my last question to you is that in the past I've read a little bit about your work, I missed— talking you anything, but I do love your work.

And you've mentioned that you find a lot of joy in mentorship, and many of us in breast cancer and in any kind of patient advocacy will we enjoy the same thing, being mentors. Have you found great way, can you recommend anything for someone who's like me who just needs patience and have been around for a while, to connect with newly diagnosed patients to help them, venture them outside of the kind of the monolith patient advocacy groups because they have a tendency to be just cliquish some of them and so like how can an individual who wants to be a patient advocate, how can she find other people to say, I'm on your team, I'm beside you. Like you said it's better to talk to someone who's already been through it, how can we best make that happen for those people out there listening that want to jump into this?

Dr. Angela DeMichele: To become a patient advocate?

Heidi Floyd: Well, yeah and to help mentor people who are just starting. I mean, it could be as simple as when you're sitting, they are waiting for chemo talk to the person sitting next to you, you know what I mean? Like if you see that they're new and scared like that's a very easy one on one but what can we do beyond that and how can we help you as doctors?

Dr. Angela DeMichele: Yeah, I think mentoring at its heart is really about walking in someone else's shoes, right? It's about helping someone see that you have gone down a path, how can they follow in that path. And that's what I love about mentoring. It's really about sharing my knowledge and my experience, my mistakes, the things I wish I'd done differently like can I help you not make those same mistakes. Can I help you know what you could be thinking about along the way, what questions you should be asking so that you can make the best decisions for yourself because so much of the time we look back and say I wish I had just thought to ask about this. So, at its heart that's what mentoring is. It's really just sharing your journey,

sharing your experience, listening and giving people the tools to try to make sure that they're asking the right questions and thinking about what they want and where some of the sort of potholes might be along the way.

And so, for those who are interested in helping other patients, there are just so many ways to do that. We have a board of patient advocates who work with us on our research. So, this isn't even at the individual patient level. This is at the research level to help us write our consent forms and make sure that they are understandable to the average person who doesn't have a medical background, that when we are designing our trials the things that we're asking people to do are reasonable in the way that we communicate about risks and benefits is understandable. This is something where we just find the input from our patient advocates to be enormously helpful, couldn't do it without them.

There's also the opportunity at all of our national meetings for advocates, people who want to be advocates to meet each other and find out about opportunities there for example at the ASCO-American Society of Clinical Oncology meeting, in June, there's an advocate's lounge somebody who has been a patient and now wants to find out how they can help be an advocate can't come to that lounge and talk to others who do this and can help them figure out how.

And at the very heart of it what you mentioned, I love love you're sitting in the waiting room, there's someone sitting there, they might look very scared or uncertain and you reach out. I cannot tell you; I care about those interactions when the patients come back to the exam rooms and say I just talked to this person in the waiting room, and she helped me so much. It was such a relief to talk to somebody. Those one-on-ones that doesn't even have to be organized but it's just that little bit of connection and kindness and empathy makes a huge difference. So there's just such a enormous range of opportunities and I just think it's amazing that as a patient you want to give back and I'm always happy to talk to patients about ways that they can do that as well. So, patients can ask their doctors how can I be a patient advocate? Can I get involved in your research or somebody else's research? Do you have anything in your Center where you could use the help of an advocate? And then of course with a professional organization also very helpful.

Heidi Floyd: Very good. That's exactly what I was hoping you would say, that's perfect. And that's how my advocacy started as well. I was pregnant when I was going through my first problem with breast cancer and young woman walked in crying also pregnant. I was like, oh my gosh, you're exactly where you're supposed to be. This doctor is amazing, and I could see it just reflected on her and I remember thinking it's almost like an endorphin to realize that because I was in the middle of this horrible horrible thing. The only way I could feel better is to make someone else feel not horrible and you want to keep giving back it's the only way to benefit. So, talk to your doctor. I think and ask or the nurses or anyone in the healthcare staff.

Dr. Angela DeMichele: Nurses also.

Heidi Floyd: Yep. Very good. Well, thank you very much.

Dr. Angela DeMichele: They will guide you to someone who can help you. They may not know the answer, but they will get you to someone who can get you that answer.

Heidi Floyd: They're always wonderful. Well, thank you. It's been an honor to talk to you. I'm really quite quite happy with we connected.

Dr. Angela DeMichele: The feeling is mutual. I really appreciate it. So great to meet you and speak with you today.

Shweta Mishra: Thank you. Thank you, Heidi, Dr. DeMichele quite an insightful conversation I must say and Heidi thank you for bringing up such important issues as diversity in clinical trials and Dr. DeMichele for addressing the struggles of clinical trial participation and how clinical trials sites that are there that will help the patients find clinical trials relevant ones and how this talking to patients like Heidi right, who have already

participated in some clinical trials can be super super helpful for people who are looking to participate. So, thank you. Thank you for all of these insights shared here. And with that it's time to wrap up the show today. We will make this talk available on your curetalks.com soon, and we also thank the University of Pennsylvania for facilitating this. Thank you.