Transcript Details
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Addressing Breast Cancer's High Recurrence Rates: The Breast Cancer Translational Center of Excellence (TCE)

Narrator:

Welcome to Medical Breakthroughs from Penn Medicine: Advancing Medicine Through Precision Diagnostics and Novel Therapies.

Dr. Mennen:

Penn Medicine's Breast Cancer Translational Center of Excellence, TCE, is known as the 2-PREVENT TCE led by Drs. Lewis Chodosh and Angela DeMichele, it aims to address one of the greatest challenges in breast cancer treatment, the high rate of relapse and late-treatment effects among breast cancer survivors. You're listening to ReachMD and I'm your host, Dr. Barry Mennen, and with me is one of the leaders, Dr. Angela DeMichele, who is the Alan and Jill Miller Endowed Chair in Breast Cancer Excellence, Professor of Medicine and Epidemiology and Co-Leader of the Breast Cancer Research Program, Abramson Cancer Center at the University of Pennsylvania School of Medicine.

Dr. DeMichele, welcome to the program.

Dr. DeMichele:

Thanks for having me.

Dr. Mennen:

Let me start off with why is breast cancer recurrence a problem?

Dr. DeMichele:

Well, we've made such tremendous strides in curing the majority of women who get a diagnosis of breast cancer, and so the good news is that over the last 30 to 40 years we have developed new approaches to surgery and chemotherapy and anti-estrogen therapies that have rendered many women free of disease; however, the problem is that up to about 20% of women who've received a diagnosis of breast cancer and been treated for it initially, will have it come back some time later in their lives. And the difficulty here is that when it does come back it can be extremely difficult to treat and is invariably fatal. So, although only 20% of women will have their breast cancer come back, 100% of women who get the diagnosis of breast cancer worry about this issue of recurrence. And, at this point in time, our ability to predict which women will have a recurrence is somewhat limited. All we can do is base that on models that estimate a risk based on the stage of cancer at diagnosis and things like the receptors. We don't have a way to actively determine whether there are still residual cancer cells after initial treatment that can lead to recurrence. So this is a time of great distress for patients. They are not only grappling with the side effects of the treatment they've received, but they're worrying about the possibility of breast cancer returning and wondering when that might happen and how they can know that this might happen.

Dr. Mennen:

How do recurrences happen? What is the underlying biology?

Dr. DeMichele:

We've learned a tremendous amount through using genetically engineered mouse models in the laboratory. Dr. Chodash and his team have recapitulated the process of going from a localized breast cancer to recurrent, metastatic disease in the mouse, and in doing so, have helped us understand the biology of this process. And so, what we've learned is that despite the fact that we're treating the primary cancer that occurs in the breast, there are seedcells, cells that essentially are quite resistant to our treatment that can escape from the breast and, essentially, lie dormant in other parts of the body. And we believe that the reservoir for these cells is primarily in the bone marrow. It's a very favorable environment for these cells that are essentially able to lie dormant, to hibernate, to remain inactive for sometimes up to several decades before something triggers them to reactivate. And what Dr. Chodash has been able to do in the laboratory is to study these cells, to understand what allows them to remain viable during this period of dormancy, what they look like so we can try to find them in patients, and what mechanism actually triggered them to reactivate. And so, by targeting both those biologic mechanisms that allow them to stay alive, as well as those that allow them to reactivate, we believe that we can now actually go after that 20% of breast cancer that's ultimately going to come back and that's what we hope is ultimately going to close the gap and help us to eventually cure every patient who gets the diagnosis.

Dr. Mennen:

That's very impressive. How can we tell that it's not a new cancer but a recurrence of an old one?

Dr. DeMichele:

Great question. Really we've learned so much by using the genetic tools that we now have at our disposal. So, we can biopsy cancers that occur at a distant site, let's say it's the bone or the lung or the liver, and we can see that there are features of those cells that are similar to the primary breast cancer that really look very much like the cancer that originally formed in the breast, but we can also see that there has been a period of transition where these cells have undergone genetic mutations that now make them fundamentally different. And what we've learned from the mouse models is that cancer in the breast, where it originally formed, cancer cells that are in this dormant phase, and then cancers that have now reached other parts of the body, all three of those types of cells are fundamentally different and they have to be treated differently from each other. So, the key now is for us to find and target these dormant cells in the marrow, and in women who have recurred to biopsy these areas of distant recurrence, and target those cancers where they now live with the unique features that will make them susceptible to our treatment.

Dr. Mennen:

What are the current monitoring options for recurrent breast cancer and what new approaches are being developed?

Dr. DeMichele:

So, for decades now we've really not had a way to look for these dormant cells, and so the current standard of care, believe it or not, is simply to have a woman monitor herself for symptoms. So, places the breast cancer typically can travel to like the lungs, the liver, the bones, we tell woman if you have a new cough, if you have new pain, if you develop a new symptom that's persistent or prolonged, you need to bring that to our attention. But there really isn't any other active way to monitor, in fact, many women say to me, "Well, aren't I going to get a scan every year?" But, in fact, there have been two studies that looked at doing scans regularly in women who've had breast cancer who have no symptoms and found that cancers were not found any earlier than they would have been had we waited for symptoms, and they weren't any more treatable if we were to find them on scan. And, in fact, doing those scans actually wasdetrimental to quality of life. And so, it is watchful waiting in a sense right now. What we're hoping now to do is, through the development of new testing approaches, be able to do a simple bone marrow test, a blood test, and be able to find the dormant cells, so

we can be screening women with these tests, actually see whether or not they have cells that could later lead to a recurrence. I think that would be really transformational in the way that we care for patients because it would empower them to know, okay, if I have these cells I'm going to go onto a trial of a treatment that potentially could take care of them, and if I don't have the cells, then I can feel an extra measure of relief that I'm doing okay. So, that's the approach that we're taking in our research center. And we've begun a large-scale screening trial for women who have had a diagnosis of breast cancer within the last 5 years, have completed all of their treatment, and are now in this followup phase. And this surveillance study allows women to come in and have a simple bone marrow aspirate done in the office in which we then test for the presence or absence of these dormant cells. And for women who have such cells, we now have a series of treatments that we're testing. And these are largely treatments that are widely available. For example, one of the treatments that appears the most promising is actually the drug hydroxychloroquine. This is a drug that has been used for decades in the treatment of infectious diseases and is actually pennies per dose, an oral drug, and we actually have found in the laboratory that it's particularly effective in a process called autophagy that enables these dormant cells to hibernate without an energy source, to essentially use their own internal energy sources. But I do think this drug that's been around for decades is very safe, is a pill. We hope that we will be able to cut off the energy supply to these cells and eradicate them from the bone marrow. And so that's just one of the approaches that we're now taking to try to actively search for these dormant cells and destroy them before they can get to other parts of the body.

Dr. Mennen:

How is recurrent breast cancer treated and what new approaches are being developed?

Dr. DeMichele:

We have an incredible number of treatments now that have really, for many women, turned this into a chronic disease and that's the good news. The good news is that if you do have recurrent breast cancer there are many things that we can do to control the disease. And so, our goal is to utilize treatments that will keep these cancer cells from growing or spreading. Can't eradicate them 100%, but it can keep them under control, often for years to decades, and these treatments might include an anti-estrogen pill, they might be targeted to other things in the cell like a receptor caller HER-2, which we use a drug called Herceptin, which is actually an antibody that induces an immune response, or it could be chemotherapy. So all of these different approaches can now be used to really control the disease. With that being said, unfortunately, each of these treatments will eventually run into the issue of resistance and resistance to treatment is a big problem with recurrent breast cancer, something that is being actively studied around the world. So, it's clear that breast cancers are not static, they're dynamic, they're constantly changing, they're constantly mutating. And what has really evolved now is a much more active approach for women with advanced breast cancer in which we are looking at the disease much more frequently via biopsies, imaging, and now actually circulating tumor cells and circulating DNA in the blood that can help us understand how the tumor is changing. And so, I think, what we're really facing is a fundamental change in our approach to advanced breast cancers where we are doing serial evaluations to understand how the disease is changing in response to therapy, what the resistance mechanisms are, and how we can best attack them. And so, when you have a choice of 10 or 15 different treatments, it's not going to be a one-size-fits-all approach and what the beauty of these new technologies is, is that we can look at the tumor, look at the tumor characteristics in an individual woman, and now tailor the treatment to what makes her tumor unique, rather than simply using the same treatment in all women which works for some and not for others.

Dr. Mennen:

If you are just tuning in you are listening to Medical Breakthroughs from Penn Medicine on ReachMD. I am your host, Dr. Barry Mennen, and I am speaking with Dr. Angela DeMichele, Co-Leader of the Breast Cancer Research Program, Abramson Cancer Center at the University of Pennsylvania School of Medicine.

So tell us about the breast cancer TCE 2-PREVENT TCE.

Dr. DeMichele:

So, the 2-PREVENT TCE was developed several years ago as a way to bring together all of the scientists and clinicians at the University

of Pennsylvania Abramson Cancer Center who are working in breast cancer with a common focus. And so, understanding that breast cancer recurrence was the main issue that's facing our patients today, we sought to develop a comprehensive approach to detecting, preventing, and better treating recurrence, if it does occur. And so, this has really evolved into a program that combined excellent clinical care for breast cancer survivors in those who've developed a recurrence, with state-of-the-art technology to help us do a better job of understanding the biology of the cancer in an individual woman, and treating it with novel therapies that are designed to target these very unique tumors. What that means, simply, is that after a woman completes her initial therapy for breast cancer and now enters the surveillance period where she'll be watched and is waiting, we want to take an active approach. Women are invited to join a program called **ACE,*14:27** which stands for Assessing the Needs of Cancer Patients after Treatment in which they enter a virtual community of breast cancer survivors. We communicate with them electronically, through our medical records. They answer a series of questions on a regular basis to help us understand how they are doing, and we have a nurse navigator who then connects them with any kind of services that they need to address issues, either related to their side effects from the treatment, to hooking them up to a nutritionist, to help with issues related to physical functioning, or even emotional and psychological counseling. So all of this is to really help women remain engaged with the oncology care team that helped them through their initial diagnosis. At the same time, this also allows women to stay engaged in the research and to participate in these new and novel approaches to looking for dormant cells and just targeting and treating these dormant cells. Moreover, we've begun a comprehensive approach to biopsying and profiling cancers when they do recur and that is called **Metamorph.*15:47** It is a program in which patients will undergo a biopsy and we do comprehensive genomic profile, almost like a fingerprint of their cancer. At the same time, we look in the blood to see if there are shed cancer cells or DNA from these cancers. All of this gives us a comprehensive picture of what that recurrent breast cancer looks like and enables us to determine whether this patient can be matched to either a clinical trial of a new therapy, or an existing therapy that's specifically going to be effective for her cancer. So, really moving from a situation where women are sort of out on their own after their initial diagnosis and treatment, to a more comprehensive approach to care that is going to enable them to stay engaged with their team, to allow us to meet their needs through this period of followup, and to enable them to become more actively engaged in monitoring for recurrent cancer. And so, I think that this is really a model that is the true essence of translational research which is we want to give excellent care, but at the same time, we can learn from every patient and we can better the treatment for the next patient, based on what we've learned from the patient who came before. And so, this integration of clinical care and research is really what our mission is all about in our 2-PREVENT TCE.

Dr. Mennen:

Now, can you share with us some of the specific research that is happening in preventing cancer and cancer recurrence?

Dr. DeMichele:

Yes. So, we have a variety of different clinical trials. I mentioned the treatment that involves the hydroxychloroquine, but we also have a variety of immunologic approaches. So, immunotherapy is certainly one of the most exciting new things that we are doing in cancer, in general, and in breast cancer specifically, and we're taking an approach with several different components. One is to develop vaccine that could be able to search and destroy these dormant cancer cells. Another approach is to develop a way to rev up the immune system so it, itself, can find these microscopic tumor cells. And thirdly, we are using other kinds of targeted therapy. A new class of drugs called cyclin-dependent kinase inhibitors, oral drugs, very few side effects, but very effective when given in addition to the anti-estrogen therapies we use. We're testing those drugs as well.

So, really coming at this problem from a variety of directions, but the common thread here is that we have a new generation of treatments that we're testing and whether they're targeting the tumor, or targeting the immune system, they are incredibly well-tolerated types of drugs that have very few side effects, do not cause people to lose their hair, do not lead to the kind of debilitating symptoms that we previously associated with cancer therapy. So, it's really an exciting time in which, not only are we finding more effective therapy, but we're also finding more tolerable therapies, so that women who have breast cancer really can go on leading normal lives. They can continue to work and take care of their children and travel and do the things that they like to do and, certainly, take care of their breast cancer at the same time. So, it's really, I think, we're on the verge of really transforming the way we think about breast cancer, from something that is debilitating and deadly to much more of a chronic disease that we can manage. Now, that's not enough, obviously, we want to eradicate it once and for all, and certainly much of the research that we do now is working towards that goal.

Dr. Mennen:

Finally, how might this TCE affect the breast cancer survivor population now and in the future?

Dr. DeMichele:

Well, I think that right now, as I said, it is a time of great distress for women when they enter the survivorship period. They have been undergoing therapy, seeing the doctor regularly, and actively dealing with that initial diagnosis of breast cancer, but now therapy is finished, the idea would be to go back and live your life and not think about the fact that you had breast cancer, but, of course, the fact is that getting a diagnosis of breast cancer is a life-changing experience. And the worry about breast cancer recurrence is really the primary thing that impacts the quality of life of women who've had the disease. So, if we can successfully use our TCE approach to be able to lead to widespread ability to test for dormant cells, to be able to tell women actively that they are clear of disease, or to help those women who have dormant cells, to eradicate them and prevent a recurrence, I think that could dramatically change life for breast cancer survivors by giving them the peace of mind that they're actively monitoring their disease, that they're actively doing something to prevent recurrence in the future. And that, I think, is really going to make a big impact on the issue of anxiety and the ability for women to be able to go on and lead normal, happy, and productive lives after diagnosis.

Dr. Mennen:

Dr. DeMichele, thank you so much for being with us today and sharing your insights.

Dr. DeMichele:

It's really been my pleasure. Thank you so much for having me.

Dr. Mennen:

I am your host, Dr. Barry Mennen. Thank you for listening.

Narrator:

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