WNPR Radio Voice 00:00:00:02 - 00:00:37:20 Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital. Welcome to Yale Cancer Answers with the director of the Yale Cancer Center, Dr. Eric Winer. Yale Cancer Answers features conversations with oncologists and specialists who are on the forefront of the battle to fight cancer. Here's Dr. Winer. Dr. Winer 00:00:38:15 - 00:01:14:28 October is Breast Cancer Awareness Month, a time to shine a spotlight on a disease that impacts essentially one in eight American women during the course of a woman's lifetime. In 2025, there will be more than 315,000 women and just under 3,000 men who will be diagnosed with invasive breast cancer. And beyond that, there are almost 60,000 women who are diagnosed with noninvasive breast cancer. Chances are, you know somebody with breast cancer. And, of course, there are many of us who have family members with breast cancer and some who have been personally affected. Dr. Winer 00:01:16:08 - 00:01:52:20 The good news is there is tremendous hope, and breast cancer survival statistics have increased progressively over the past two to three decades. Advances both related to early detection and treatment have made a huge difference. And there are now over 4 million breast cancer survivors in the United States. So now that it's October, we're going to spend half an hour tonight talking about breast cancer treatment, breast cancer screening, breast cancer prevention. Dr. Winer 00:01:52:20 - 00:02:25:19 And with us tonight is Dr. Maryam Lustberg. Dr. Lustberg is a professor of medicine in medical oncology at the Yale Cancer Center. She is the chief of the Division of Breast Oncology and is a well-known international expert on the management of patients who have breast cancer. Miriam, thanks so much for joining us tonight. Dr. Lustberg 00:02:25:19 - 00:02:53:12 Glad to be here tonight. Thank you. Dr. Winer Maybe we could just start with you telling us how the—how did you find yourself going into breast cancer? There are a lot of different areas that oncologists get interested in, and I'm not going to take this back to how you decided to become an oncologist, but given various different types of cancers, what made you want to be a breast cancer doctor? Dr. Lustberg 00:02:54:12 - 00:03:40:20 Yes, my interest was piqued during medical school and internal medicine residency when I had an opportunity to shadow several breast oncologists. And what was most meaningful to me was the interactions with patients and their families and the close relationships that were formed, and wanting to have that in the future. So that was a primary driver of that decision, followed by seeing, even 20 years ago, just how much active research was ongoing in breast cancer and seeing how rapidly the field was moving forward and wanting to play a small role in that. Dr. Winer 00:03:41:29 - 00:04:13:01 Well, I think you've played more than a small role. And as a breast cancer doctor myself, I can say that it's an area that I have felt is always interesting. Taking care of patients with breast cancer is something that I personally have enjoyed and, to this day—not that I want anyone to have a new diagnosis of breast cancer—but I always enjoy seeing every new patient. It's like a new experience whenever it happens. And I suspect you feel the same way. Dr. Lustberg 00:04:13:01 - 00:04:41:07 I do. I do. Dr. Winer So maybe you could help us understand the different types of breast cancer, because back 30 years ago, a woman would say, "What kind of breast cancer

do I have?" And I, at least, would say, "Well, you have stage one breast cancer, stage two breast cancer, stage three breast cancer." But in truth, that says how much cancer there is. It doesn't say anything about the type of breast cancer or what I sometimes call the "personality" of the cancer. And so, tell us about the different types of breast cancer. Dr. Lustberg 00:04:41:07 - 00:05:21:03 Yes. So I think this has been one of the many remarkable advances in breast cancer: our understanding that it's not just one cancer type, but that there are at least, clinically, three different subtypes that we use actively, clinically, as we see patients. And these are routinely available to us as clinicians from a simple pathology report. This has remarkably changed how we practice and how we personalize our treatments. About two-thirds of our breast tumors are what we call hormone receptor-positive breast tumors, and we have wonderful endocrine therapies or anti-estrogen targeted therapies for managing these breast cancers.

Dr. Lustberg 00:05:21:03 - 00:05:52:02 And this is, as I mentioned, two-thirds of all our breast cancers. And then we have about 15% of our breast cancers that have an extra reporting or antennas, I like to call it, called HER2, which tend to be faster-growing. These used to be known as one of our most aggressive types of breast cancer, but now, with advances in treatment, they're actually one of our best-treatable types of breast cancer. Dr. Lustberg And third, we have a set of breast cancers that neither express hormone receptors nor HER2, and we call those triple-negative. And there have been lots of advances in this area as well. Dr. Winer 00:05:52:14 - 00:06:20:15 So we call them for what they're not, not what they are. Dr. Lustberg Exactly. Because they're negative for estrogen and progesterone receptors and negative for HER2. Dr. Winer Yes. And so these subtypes affect how we approach treatment decisions, at least medical treatment decisions. To what extent do they affect decisions about local therapy? So whether a woman has a lumpectomy or a mastectomy—do they play much of a role there? Dr. Lustberg 00:06:20:22 - 00:07:41:04 Not as much, but they do certainly impact the timing of when we deliver our local or regional therapies. By that, I mean that HER2-positive tumors and triple-negative tumors that are at least stage two or stage three—many of these now benefit from preoperative systemic therapy before going to surgery, whereas with hormone receptor-positive tumors, we tend to elect to proceed to surgery first. So it's more the timing of how we deliver our local regional therapies and less the type of surgery. The type of surgery is determined by the extent of disease, genetic factors, and patient choice. So all of those determine the type of surgery that's planned. Dr. Winer And, you know, I touched on these issues about local therapy with one of our surgical colleagues some number of months ago. But can you comment on the, what I'll call, the sort of immediate reaction that some patients have when they hear they have breast cancer—that they just want to have both their breasts removed, you know, just be done with it and take the most aggressive surgical approach? Is that something that people should be rushing to do? Dr. Lustberg 00:07:41:04 - 00:09:17:18 It's a very human reaction. It's a human response to being told very surprising and obviously distressing news. However, we have a large body of data matured over decades that

really have shown that more surgery is not necessarily more positively impactful. We know that breast-conserving surgery, along with lumpectomy, gives patients equivalent long-term outcomes to mastectomy, and there's really no data that removing an unaffected breast is going to help you live longer. So, ultimately, I do believe it is an individual's choice what type of surgery they have. However, I think not making those decisions out of distress and fear, and knowing the facts, is important. Jumping to a bilateral mastectomy is not necessarily going to be the best choice for every patient. Dr. Winer And there are perhaps a few exceptions to that, which we'll get to in just a minute when we talk about genetics. So before talking more about treatment, maybe we could talk about risk factors and about genetic predisposition. So, apart from a genetic predisposition, what are some of the risk factors—apart from just being a woman, since we know that by definition, being a woman places you at dramatically higher chances of getting breast cancer than your male counterpart? Dr. Lustberg 00:09:17:19 - 00:11:01:19 Yes. Being female is, as you know, the biggest risk factor. Growing older—so we know that the risk of breast cancer rises with each decade of life, although younger women, as we know, can still develop breast cancer. And it's important to have an awareness of that. Hormonal exposure—the timing of menarche and the time that you enter menopause—so the length of the decades of life that you've been exposed to different hormones, timing of pregnancy, exposure to hormone replacement therapy, particularly combination hormone replacement therapy, and the duration of exposure can all be risk factors. And then there are lifestyle factors—obesity, particularly in post-menopausal years, sedentary behavior, limited physical activity. All of these, including smoking, are modifiable risk factors that can impact breast cancer risk. And then, of course, we'll talk about the hereditary risk factors—the genetic risk factors that you inherit from your parents. And those actually account for less than 10% of our breast cancers. Dr. Winer 00:11:01:19 - 00:12:12:18 And there was a lot in the news over the last year about alcohol and breast cancer. No matter what one might say about the risks of having one drink or even two drinks occasionally—although the recommendation in the United States is for women to not exceed having one alcoholic beverage per day—there was this suggestion that any alcohol intake might increase risk. I think there's been some debate about that. What there's no question about is that heavy alcohol intake clearly does increase the risk. Dr. Lustberg Absolutely. I think it's really important to be aware of these associations that we see in large epidemiological studies, but also interpret them within the context of what they're showing us. A few alcoholic drinks per week very minimally elevate risk. So each individual woman can make that decision herself, but the risk elevation is quite small for those few drinks. Dr. Winer 00:12:12:18 - 00:13:10:21 So let's just spend a minute or so before we have to break talking about BRCA1 and BRCA2, which are certainly the biggest genetic risk factors in terms of developing breast cancer. Tell us a little bit about that. Dr. Lustberg 00:13:10:21 - 00:14:30:00 So less than 10% of our diagnosed breast cancers are associated with BRCA1 and 2. They're known as highly penetrant genes. They are involved in DNA repair pathways, and when they are altered, they elevate the lifetime risk of developing breast cancer as well

as other cancers such as ovarian cancer, GI cancers, and skin cancers. Knowing this information is important in terms of making certain decisions about breast cancer treatment. Given that elevated lifetime risk, some patients—but not all—with BRCA alterations may choose to have prophylactic breast surgery on the unaffected side. Others may choose to do more intensive surveillance with breast MRI and mammogram. Dr. Lustberg 00:14:30:00 - 00:15:02:23 And then I think the important risk of ovarian cancer—because we do not have effective screening tools for ovarian cancer—risk-reducing oophorectomy before the age of 40 is recommended. And as patients get older, we do recommend that they undergo pancreatic cancer screening. We recommend routine skin checks, etc. So knowing this information is important in terms of making some proactive decisions. For certain triple-negative and hormone receptor-positive tumors, knowing this information can also impact our ability to administer certain targeted therapies that are specifically for our patients with these alterations. Dr. Winer 00:15:03:02 - 00:15:44:18 So it's important information to have as you make these decisions with your oncology teams. And more and more, we do genetic testing in a large number—and maybe not everyone—but in a large number of patients who come in with a new diagnosis of breast cancer. Well, we're going to have to take just a very quick break, and we will be back in a minute with our guest tonight, Dr. Maryam Lustberg, chief of the Division of Breast Oncology at Yale School of Medicine. WNPR Radio Voice 00:15:45:00 - 00:16:13:01 Funding for Yale Cancer Answers comes from Smilow Cancer Hospital, where nationally renowned breast cancer specialists deliver compassionate, cutting-edge care. Learn more about innovative treatment options at SmilowCancerHospital.org. There are many obstacles to face when quitting smoking, as smoking involves the potent drug nicotine. Quitting smoking is a very important lifestyle change, especially for patients undergoing cancer treatment, as it's been shown to positively impact response to treatment, decrease the likelihood that patients will develop second malignancies, and increase rates of survival. Tobacco treatment programs are currently being offered at federally designated comprehensive cancer centers such as Yale Cancer Center and Smilow Cancer Hospital. All treatment components are evidence-based, and patients are treated with FDA-approved first-line medications, as well as smoking cessation counseling that stresses appropriate coping skills. More information is available at YaleCancerCenter.org. You're listening to Connecticut Public Radio. Dr. Winer 00:16:42:17 - 00:17:11:07 Hello again. This is Eric Winer, returning for the second half of Yale Cancer Answers. I'm very pleased to be here tonight with my colleague, Dr. Maryam Lustberg, chief of the Division of Breast Oncology. And we're talking about breast cancer. This is October, and it's Breast Cancer Awareness Month—talking about risk factors for breast cancer and some treatment issues. And if we have time, we'll even touch on screening. But we'll have to see. Maybe we can talk a little bit about all the progress that has been made, because the past two to three decades have really been quite remarkable. And I would say mostly the past two decades—both in terms of the development of new treatments and also our ability to eliminate some treatments that perhaps aren't as effective in some patients as others. So the ability to be able to stream-

line the treatment for a lot of people. Dr. Winer 00:17:45:00 - 00:18:14:23 Tell us a little bit about some of the treatment advances. Dr. Lustberg 00:18:14:23 - 00:19:12:06 I think our ability to be able to speak to an individual diagnosed with hormone receptor-positive breast cancer and be able to tell them with good objective data whether they would benefit from chemotherapy or not is remarkable. I think I'm old enough that the studies—when they were just prospective studies, like the TAILORx trial—were ongoing when I was a medical oncology fellow. It is such a remarkable advance to be able to take a piece of tumor tissue, send it, and get a report back that gives us prognostic information about the biology of the breast cancer—how hormonally driven it is—and then secondarily, to be able to know whether there is benefit to the addition of chemotherapy. These genomic tests have really revolutionized how we treat hormone receptor-positive breast cancer and led to a dramatic reduction in the use of chemotherapy in patients who didn't need it, while still obviously giving chemotherapy to those individuals who do need it. Dr. Lustberg 00:19:12:06 - 00:19:44:18 So this type of personalized precision medicine, which sounds so sci-fi, is really happening. I get to look at a report and discuss it with my patients and make much more informed decisions about what type of systemic therapy to give. Dr. Winer And 25 years ago, there was a consensus conference at the National Cancer Institute where it was concluded that any woman who had a tumor greater than a centimeter or had positive lymph nodes should automatically get chemotherapy. Thankfully, now the question isn't who can we omit chemotherapy from—it's really who needs it. Because it's the minority of patients with hormone receptor-positive breast cancer who ultimately get a big benefit from chemotherapy. And so we've really done much better there, developing, as I said, more streamlined approaches. Dr. Winer 00:19:44:18 - 00:20:17:06 What about in the setting of HER2-positive breast cancer? You alluded to that earlier. What's been the big change there? Dr. Lustberg 00:20:17:06 - 00:21:32:03 Completely revolutionary. The discovery of trastuzumab, which is a HER2-based monoclonal antibody in combination with chemotherapy, has completely changed the course of these HER2-positive tumors. The story of HER2-positive disease really tells the story of very stepwise, thoughtful clinical trials that have led to what we call de-escalation—or rightsizing—our therapies. We started out with much more intensive regimens, and over time, this has led to smarter, shorter, more thoughtful regimens that still have similar efficacy. And the story continues. Now we're thinking about newer ways of delivering these types of HER2-targeted therapies through technologies known as antibody-drug conjugates. It's quite a remarkable story of using advances in clinical trials to truly change the course of the disease. Dr. Winer 00:21:32:25 - 00:22:03:21 And then there's immunotherapy. Immunotherapy plays what role in breast cancer? Dr. Lustberg 00:22:03:21 - 00:22:32:24 Breast cancer, compared to some of the other cancer types, was a little bit later into the immunotherapy game, with our first indication being in triple-negative breast cancer, where immunotherapy in combination with chemotherapy was shown to have improved outcomes in both metastatic triple-negative breast cancer as well as stage two and stage three triple-negative breast cancer. So, very important advances for this subtype of

breast cancer. And we're continuing to think about newer immunotherapy combinations and new ways to give these drugs more safely. There's also a whole body of efforts looking at how immunotherapy could be administered to other subtypes of breast cancer. For example, there may be a subset of hormone receptor-positive tumors that may benefit. So, I think the story of the expansion of immunotherapy use in breast cancer is going to continue to evolve. Dr. Winer 00:22:32:24 - 00:23:02:04 And all of this stems from clinical trials, since no drug goes from the laboratory to the clinic without a big clinical trial step. And, you know, thankfully, women with breast cancer—and occasionally men—have stepped forward to volunteer for clinical trials that have sometimes helped them individually. And other times, hopefully, it has not hurt them, but it has helped us answer questions. And those are really critical. Even in the setting of patients who have advanced breast cancer, or what's called metastatic breast cancer, people are living far longer than they used to. They're living far better lives. And I'm sure this is something you've seen in your career. Dr. Lustberg 00:23:02:04 - 00:24:08:06 Absolutely. I think we have the emergence of very specific targeted therapies, where in combination—for example, the use of a set of drugs known as cyclin-dependent kinase inhibitors—they augment the efficacy of our traditional endocrine therapy agents and have really dramatically improved outcomes in hormone receptor-positive breast cancer. But another major advance is that we're actually using tumor sequencing to find very specific actionable, targetable pathways. And we have drugs for them now. So it's not just knowing for the sake of knowing, but we have actionable targets. Every day, I can look at a sequencing report and potentially find a pathway that I can offer to my patients, either on a clinical trial or as part of standard of care. All of this, I think, is dramatically different than when I first started practicing two decades ago. Dr. Winer 00:24:08:06 - 00:24:33:29 So I said that we might get to screening. But I'm struck that, since this is Breast Cancer Awareness Month, and since most of our listeners are not people who have had breast cancer but are people who are potentially at risk and have screening, we should actually provide some guidance about screening. And of course, we all know that screening isn't perfect. We want it to get better and better. But in 2025, how do you advise the average-risk woman in terms of when she should start screening, how often she should get it, and when she should stop doing screening? Dr. Winer 00:24:33:29 - 00:24:59:21 And I realize that this is somewhat debatable and that different groups have different recommendations. But give us a general sense of what you would tell your sister or mother. Dr. Lustberg 00:24:59:21 - 00:26:18:10 So, first, knowing your risk is important. An average-risk individual in the U.S. would be somebody without a primary direct relative with breast cancer, no prior history of breast cancers. This average-risk woman, the recommendations have actually converged to start screening at age 40. There used to be intense debate about whether it should be 50 versus 40. But at least one of the advances in 2024 was that all the societies have converged on age 40 as being the starting age of screening. Where some of the guidelines may differ is whether it should be every two years or every year. So we like to say every one to two years and continuing until at least up to age 75, knowing that that's

where our clinical trial data on screening essentially ends. After that, we make informed decisions about what are your competing health factors, how good a health you're in, and kind of making individual decisions for screening past age 75. Dr. Lustberg 00:26:18:10 - 00:26:43:21 Generally, most patients would receive a mammogram, knowing that knowing your breast density—which is now a federal law—every mammogram report will have a paragraph at the bottom that tells you about your breast density. Then, having conversations with your doctor about what are the implications. About half the patients in the U.S. will have higher breast density, and some of them may choose to have additional supplemental imaging. But all of that can be discussed with your clinical teams to make the right decision for you. Dr. Winer 00:26:43:21 - 00:27:17:00 And finally, just before we wrap up, breast cancer prevention is a pretty hard nut to crack. Do you think that we're going to be any closer to preventing breast cancer in the next five to ten years? And where do you think we'll be in 20 or 30 years? Dr. Lustberg 00:27:17:00 - 00:28:20:25 I don't know. I don't know. I think it's going to be a multipronged effort with lifestyle factors—improving our metabolic health and fitness. But there's also a wonderful body of work looking at preventative vaccines that are nowhere near ready for primetime. But who knows? Maybe in ten years they would be. And also advances in our imaging—can we use imaging, combined with artificial intelligence analytics, to better predict who might be at higher risk versus not? I think all of these will converge in the next five to ten years, and at least we would be able to give more precise information to women who we are seeing in a high-risk clinic. Dr. Winer 00:28:20:25 - 00:28:50:19 Dr. Maryam Lustberg is a professor of internal medicine and medical oncology at the Yale School of Medicine. If you have questions, the address is CancerAnswers@Yale.edu, and past editions of the program are available in audio and written form at YaleCancerCenter.org. WNPR Radio Voice 00:28:51:04 - 00:28:59:00 We hope you'll join us next time to learn more about the fight against cancer. Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.