

Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Miller is a medical oncologist specializing in pain and palliative care, and he also serves as the Director of the Connecticut Challenge Survivorship Clinic. If you would like to join the discussion you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This evening Dr. Chu and Dr. Miller are joined by Dr. Maysa Abu-Khalaf and Gina Chung. Drs. Abu-Khalaf and Chung are Assistant Professors of Medical Oncology and leaders of several clinical trials for breast cancer at Yale Cancer Center.

- Chu How common is breast cancer in the United States?
- Abu-Khalaf Breast cancer is very common. About 1 in 8 women are expected to have breast cancer during their lifetime. It is the most common cancer in women, and therefore, it is very important for patients to be screened.
- Miller About how many thousands of women will be diagnosed with cancer?
- Abu-Khalaf About 200,000 women will be diagnosed in the US every year with breast cancer.
- Miller In terms of cancer related deaths, is it also a significant problem?
- Chung It is. It is the second most common cause of cancer related deaths in US women, second behind lung cancer. As Dr. Abu-Khalaf said, it is a very, very common and prevalent disease.
- Miller I want to ask you about screening. We have a lot of woman listening to this show right now, what message do you want to get across to them about what the optimum screening is?
- Abu-Khalaf The recommended screening for patients is that at age 40 they start having a yearly mammogram. For women who are at a higher risk for breast cancer, those that have a strong family history with first-degree relatives or carry genetic mutations, it starts as early as 25 years of age, or 5 to 10 years before the first-degree relative developed breast cancer. The reason we recommend screening is because it improves survival. If it is detected earlier rather than later, there is a higher chance of cure.
- Chu There has been some discussion, or controversy, as to whether or not mammography is the ideal imaging technique. Are there are any other imaging modalities that may be better than mammography, or is mammography still the gold standard?

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- Chung In this day and age we really do need to still emphasize that the primary screening modality for breast cancer remains mammography. There are other exciting and newer modalities, for example MRIs of the breast, which are a very important tool as well. But at this point, it is still reserved for certain circumstances. For example, perhaps in patients, as Maysa mentioned, with genetic mutations such as the BRCA gene. It still should be done in conjunction with mammograms, so it is not a replacement for mammograms and that is really important to emphasize. It has strengths, but it also has weaknesses. Although it may be more sensitive at detecting certain lesions compared to mammograms, it does have a higher false positive rate, so that needs to be taken into consideration as well.
- Chu On the low tech side of things, how about breast self-exam and exam by doctors, how often should those be done?
- Abu-Khalaf That is controversial as well. However, for the most part we do recommend breast self-examinations for adult women and certainly a clinical examination should be performed regularly as well. For adult women and premenopausal women we recommend that self-exams be performed shortly after the menstrual period.
- Chu Both of you have mentioned BRCA-1, the genetic mutations that have been linked to breast cancer, and obviously for women there is a lot of anxiety about whether or not genetic testing should be done. In what setting would one think about doing genetic testing for breast cancer?
- Abu-Khalaf It is very important to know that most cancers are not due to genetic mutations; about 5% to 10% of breast cancers are due to genetic mutations. Red flags that make us think about testing, or at least counseling, are younger patients, younger than 40 or 45 years of age, that have multiple family members, including first-degree relatives, family history of ovarian cancer and breast cancer, or men in the family that have had breast cancer. Sometimes just young age by itself is a red flag that there might be something more. At Yale-New Haven Hospital, when we see patients in our clinics and suspect that there might be a genetic mutation with a strong family history or young age, we refer our patients for genetic counseling. When they meet with members of the genetic team they discuss their risk factors, their family history, and then after that discussion it is decided whether there is really a need for testing.
- Miller Gina, when you see a new patient who is diagnosed with breast cancer, let's say it is early stage breast cancer, what are the factors that you look at for that patient as you start to think about what you are going to do for her?

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- Chung It is a good question. The approach is multi-pronged. We look at the specific features of that patient's tumor first, very important is stage, and that is a measurement of how big the tumor is and how far the tumor may have spread in the body. That is one very important factor in prognosis, which obviously has implications in treatment for the patient. In addition, there are certain biologic features of the tumor that are very important in prognosis and treatment as well. For example, in breast cancer, we routinely test the status of the estrogen receptor, or the ER status, as well as the progesterone receptor or PR, and the HER2/neu protein, These things are all very important because we have treatments targeted directly at these proteins, for example, tamoxifen for ER positive disease and Herceptin for HER2/neu positive disease. It is also very important to remember that the patient is a person and we look at the functionality, the age, and other medical problems that the patient has before we come up with an overall treatment plan.
- Chu For early stage breast cancer it really is a team-based approach, right? Maysa, can you help us go through that in terms of what disciplines are involved other than medical oncology in coming up with a treatment plan?
- Abu-Khalaf The physicians that are usually involved from the start are the medical oncologist, the surgical oncologist, and the radiation oncologist. In the past few years there has been a lot of emphasis on a multi-disciplinary approach where we often meet with the patient on the same day and then as a team we discuss what our thoughts are about treatment options. Then we discuss the new cases, especially at our Breast Cancer Tumor Board where we have our colleagues from radiology and pathology and other members of the medical oncology, surgical oncology, and radiation oncology come up with a plan. Then we meet again with the patient and we discuss the recommendations, and of course, we take into account what the patient's wishes are.
- Miller I want to ask a couple of truth or myth questions. Gina, is this truth or myth, that all patients with breast cancer need chemotherapy after surgery?
- Chung I would say that is a myth.
- Miller We thought so, but why?
- Chung Well, again, going back to what I said earlier, it is very important to look at an individual patient's tumor characteristics, and the patient as a person. For some patient's breast cancer, for example let's say a stage 1, small, less than 1 cm breast cancer, we have been giving chemotherapy over the last 10, 15, 20 years, more and more for patients with early stage breast cancer, there are clearly a subset of patients with good enough

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prognosis for alternative treatments in the form of hormonal therapies like tamoxifen, where I think chemotherapy would have very little to add.

Miller Maysa, truth or myth, mastectomy is better than lumpectomy and radiation?

Abu-Khalaf Myth.

Miller All right.

Abu-Khalaf A lot of the patients come in and their first inclination is “I want the breast removed,” thinking that’s going to improve their survival. There has been extensive data that breast conservation surgery, with a partial mastectomy, or what we call a lumpectomy, with the addition of radiation therapy has similar survival. Often our treatment is focused on the local recurrences, or what we call recurrences in the breast, and radiation therapy helps with that as well. Most of the time as a medical oncologist, our discussions are also about reducing recurrences that are distant. These are more serious recurrences and the mastectomy would not necessarily help with that, and that’s why we talk about chemotherapy and hormonal therapy to try to reduce the risk of the cancer coming back outside the breast and the lymph nodes, such as in organs like the lung or the liver, and the mastectomy would not necessarily help with that.

Chu Is it always the case that if the breast cancer is localized to the breast, or has not spread to other tissues in the body, that surgery is always done, or are there any instances in which one might consider giving chemotherapy, hormonal therapy, or a combination plus or minus radiation therapy beforehand?

Abu-Khalaf What you are talking about is what we call preoperative chemotherapy, or hormonal therapy. The standard has been that when we are able to remove the cancer, we remove it and then we follow it up with radiation therapy when needed, and then we talk about chemotherapy and hormonal therapy. However, there are cases where the cancer, although localized to the breasts or lymph nodes, is large and the surgeon might have difficulty removing the whole cancer without leaving anything behind. There are also cases where the cancer is large enough and where the surgeon might not be able to remove it and preserve the breast, so there are instances where a mastectomy might have been the only alternative, but now, with giving chemotherapy upfront, we might shrink it and be able to preserve the breast and do only a lumpectomy instead.

Miller We have an email question regarding this. This is from Phyllis who lives in Middletown, and she says, “*I was found to have breast cancer and the doctor is recommending that I*

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receive chemotherapy before surgery. Do I need to worry about leaving the cancer there in the meantime?"

Chu Gina, your thoughts

Chung I can understand the hesitancy and unease of certain patients, but we think that delivering what we call systemic therapy, usually in the form of chemotherapy but sometimes with hormonal therapy and other drugs, is actually a plus in breast cancer. Breast cancer is a disease that we think of as often being found localized in the breast, but can potentially, what we call, micrometastasize, very early on. That is, minute cancer cells may actually break off and travel through the blood and the lymph stream and spread out quite early on in the growth of the breast cancer. Thus, delivering drugs that can actually target and kill these microscopic cells, as well as the bulk of the tumor in the palpable tumor let's say, is actually a good thing. It is certainly not something that is addressed when you go to surgery first, and the reality is when you give, for example, combination chemotherapy first before surgery, the vast majority of patients actually have a good response, and shrinkage of the tumor. It is really not a question of is it going to shrink or not, but how much is it going to shrink? A minority of patients, perhaps about 20% to 30% of patients, will have what we call a pathologic complete response.

Miller You are listening to the Yale Cancer Center Answers. We are here discussing the latest in treatment and clinical trials for breast cancer with Dr. Maysa Abu-Khalaf and Dr. Gina Chung.

Medical Minute

Over a 170,000 Americans will be diagnosed with lung cancer this year and more than 85% of these diagnoses are related to smoking. The important thing to understand is that quitting, even after decades of use, can significantly reduce your risk of developing lung cancer. Now, everyday, patients with lung cancer are surviving thanks to increased access to advanced therapies and specialized care, and new treatment options are giving lung cancer survivors new hope. Clinical trials are currently underway at Federally designated Comprehensive Cancer Centers like the one at Yale to test innovative new treatments for lung cancer, and patients enrolled in these trials are given access to medicines not yet approved by the Food & Drug Administration. This has been a medical minute, and you will find more information at [yalecancercenter.org](http://www.yalecancercenter.org). You are listening to the WNPR Health Forum from Connecticut Public Radio.

Miller Welcome back to Yale Cancer Center Answers. This is Dr. Ken Miller and I am joined

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by my co-host Dr. Ed Chu, and also our guests Dr. Maysa Abu-Khalaf and Dr. Gina Chung from the Yale Cancer Center. Let's focus on some of the work that you are doing which I think is very, very exciting. Gina, you are working on research now on giving preoperative hormonal therapy. Can you tell us about that?

Chung We have known, and alluded to earlier, that in patients who have estrogen receptor positive breast cancer, which represents about 60% to 75% of breast cancers, those patients often have a very good response, and sometimes a better response with hormonal therapy such as tamoxifen or aromatase inhibitors than even chemotherapy. Thus the question was, and we already talked about chemotherapy shrinking breast tumors before surgery, but can we actually get a better response, or at least an additive response, by adding hormonal therapy? Our clinical trial is recruiting patients who have ER positive breast cancer, in this case they must be postmenopausal because the hormonal therapy of choice is something called letrozole which is an aromatase inhibitor that is effective in postmenopausal women. In addition, we will be combining this drug with a drug called Avastin, or bevacizumab. This is a monoclonal antibody therapy that is targeted against a protein that we think is very important in angiogenesis called VEGF, and the combination is felt to be more effective than individual drugs on its own. So patients will be getting the two drugs in combination for approximately four months before surgery with the goal of shrinking the tumor prior to surgery.

Chu And one of the nice things about this combination, I take it, it is that there are relatively fewer side effects than compared to traditional chemotherapy.

Chung Yes, absolutely, and one of the hopes to underline is that if patients have very good responses and good long-term outcomes, perhaps there are patients we can tease out who can avoid chemotherapy that may have otherwise received it. And yes, the hormonal therapy, and Avastin in general, have much more tolerable side effects, the most common being things like hot flashes for the hormonal therapy that are not too bad, no hair loss, etc.

Chu Gina, you have also been very focused on trying to target this process of angiogenesis that you just mentioned, can you tell our listeners out there why this process of angiogenesis is so important and why you are focused on trying to inhibit that process?

Chung Cancer growth, including breast cancer, is obviously a very complicated process and there are many, many things that are very important in the development, growth and spread of cancer. One of the things that has really come to light recently is this process of angiogenesis, which is the formation of blood vessels in and around tumors. There are

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many hypotheses as to why this is important, and of course, if it is really important the next question is, how can we stage this process so that we can take advantage of it as a treatment modality. When we look at tumors, we can actually see more blood vessels around it, and it may be that these blood vessels are serving to bring in more nutrients and oxygen to help the tumor grow, but perhaps also what we can do is give treatments that can take advantage of that, so treatments are delivered to the tumor better. This is a very exciting field and there are certainly many, many drugs currently available, Avastin being one of them, but there are others in development targeting this very important pathway.

Miller Maysa, I know you have done some very interesting work related to Herceptin, which is a target therapy. Tell us a little bit about that, and what are you working on now?

Abu-Khalaf Herceptin is a very important drug. As Dr. Chung talked about, in the past having an expression of HER2 protein on breast cancer cells led to a worse prognosis, so patients had worse outcomes. Then the drug which targets these proteins and blocks the pathway that causes the worse prognosis in breast cancer, led to improved survival, and this was initially evaluated in patients with advanced breast cancer. Most recently, there has been a lot of data that supports giving it upfront for early stage breast cancer. However, we know that a small percent of patients are resistant to Herceptin upfront, and a lot more become resistant later during treatment. Given the importance of this drug, and this pathway, we have decided to look at other drugs that might reverse the resistance to Herceptin. We have a drug called rapamycin, which comes under the category of an mTOR inhibitor, and this is a drug that's been studied in organ transplant extensively. More recently, it has been found to have effects on cancer biology, so what we are trying to look at in clinical trials is whether we can reverse the resistance of Herceptin. One method to do this is to evaluate whether this mTOR inhibitor called rapamycin can do so.

Chu What is really remarkable, as we learn more and more about the biology of cancers in general, but specifically breast cancer, is that breast tumors have an amazing way of adapting once we give a certain treatment. There are so many different ways for the breast tumor to continue to grow even in their presence. This is one interesting approach to try to target the ability, or inhibit the ability, of the breast cancer to overcome our treatments.

Chung Yes, I think the major advances in breast cancer have come from our understanding that not all breast cancers are the same. Even within the subtypes like HER2 positive, or ER, PR positive cancers, there is variation in how these tumors respond and how they find ways to overcome, or become resistant to, the available drugs. It is very important that we use these novel drugs that we have to try to overcome this resistance.

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- Miller What other new agents are you working on right now, Maysa?
- Abu-Khalaf We have another clinical trial that we will be opening up soon looking at a drug called vorinostat. It is one of the groups that are called HDAC inhibitors, and again, we are using this with a drug called capecitabine that has been proven to have effects in advanced breast cancer. What we are doing is looking at different schedules of capecitabine, or Xeloda, in combination with vorinostat with the hope that we will find synergy and improve efficacy in treatment of these patients.
- Miller Question for both of you, we have talked a lot about targeted therapies, is there anything new or different in terms of using chemotherapy for women with metastatic breast cancer? Any advances that you have found to be exciting?
- Abu-Khalaf You mean chemotherapy targeted therapy?
- Miller Chemotherapy or combining chemotherapy and target it.
- Chung There is actually a number of them and there are always many ongoing clinical trials looking at novel therapies in metastatic breast cancer, as well as novel combinations and novel chemotherapies as well. For example, a drug called ixabepalone, which falls under a category called epothilones, is a chemotherapy and has been recently approved for use in combination with capecitabine in metastatic breast cancer. There are a number of other combinations, for example, taxanes and taxol with Avastin, the antiangiogenesis targeted agent, and that's been approved for metastatic breast cancer recently as well. There are very interesting drugs that are being approved and many others that are being studied currently.
- Chu I think an important point to emphasize is that the treatment of advanced breast cancer really has evolved and matured over the last few years, such that I think it's fair to say that women with metastatic breast cancer really are dealing with a chronic disease, and perhaps colorectal cancer is next in line. There are so many treatment options available, first line, second line, third line, fourth line, chemotherapy, biologic agents and targeted agents, that certainly since Ken and I were in training, back in the dark ages, things have moved over the last 10 or 15 years. It's really amazing, the advances that we have seen, wouldn't you say?
- Abu-Khalaf It's a very exciting time and we have a lot more novel drugs on the way, so even with what we have right now, we have a lot more to offer to patients. There are a lot of choices, and often it's confusing for patients to have so many choices, but I always tell

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my patients it's a good thing to have all these options.

Miller Just as a final question, and a very broad one, if you see a new patient with breast cancer, and they ask you if it's a curable disease, what's your answer?

Abu-Khalaf Yes, it is definitely a curable disease. That's why we encourage screening because the earlier the diagnosis, the higher the cure rate.

Chu Great, Maysa and Gina, it's been great having you on the show and we look forward to having you back and telling us what advances have been made on the clinical trials front. You have been listening to Yale Cancer Center Answers. We would like to thank our guests, Drs. Maysa Abu-Khalaf and Gina Chung for joining us this evening. Until next time, I am Ed Chu from the Yale Cancer Center wishing you a safe and healthy week.

If you have questions for the doctors or would like to share your comments, go to yalecancercenter.org where you can also subscribe to our podcast and find written transcripts of past programs. Next week you will meet Dr. Otis Brawley, Chief Medical Officer for the American Cancer Society. I am Bruce Barber and you are listening to the WNPR Health Forum from Connecticut Public Radio.