

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 is 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 188-234-4YCC. This evening Dr. Chu speaks with Dr. Lindsay Harris and Dr. Gina Chung about new treatment options in breast cancer. Dr. Harris is the Director of the Yale cancer Center Breast Cancer Program and Dr. Chung is the Assistant Professor of Medical Oncology at Yale Cancer Center.

Chu Lyndsay, lets start off with a brief overview. How significant is breast cancer as a public health issue?

Harris Unfortunately, breast cancer is a very common disease. We estimate that if a woman lives to the age of 85 she has about a 1 in 8 risk of developing breast cancer in her lifetime. About 200,000 or more cases per year are diagnosed.

Chu Wow, and in terms of cancer related mortality, how many deaths would be attributed to this disease each year?

Harris Fortunately those numbers have improved quite substantially and the number of women who actually die from the disease is less than 30% of the overall number of women who are diagnosed every year. At least 70% of women with a breast cancer diagnosis are cured.

Chu I gathered from some recent reports that in fact the survival rates have actually improved over the last few years. Is that correct?

Harris That is absolutely right, and in fact, it appears that the survival improvement is due not only to early detection and screening, but also therapies that have been developed in the last 15 to 20 years that have truly impacted survival.

Chu A little later on in show we will get into more of these new target therapies that have made a tremendous difference in treating women with breast cancer. What age group do we tend to think about for when breast cancer can develop?

Chung Breast cancer is more common as we age. Although we all may know of people who were diagnosed at a young age, it is typically diagnosed more in the postmenopausal age groups, so 50+ and 60+. However, we do know that breast cancer certainly can be diagnosed earlier as well, and so screening is initiated earlier than the postmenopausal age category.

Chu How about if there is a strong family history of breast cancer? Does

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breast cancer then typically occur at an earlier age in that setting, or it is still the same age risk?

Chung We know family history is a very important risk factor for breast cancer development, although, probably only about 10% or so of breast cancer diagnoses are directly impacted by genetic risk factors and a strong family history. It is clearly a very important risk factor and in those women who are diagnosed with breast cancer, and have very strong family histories, we do advocate genetic counseling to assess what those risk factors are more directly, and perhaps test for genes that may be involved.

Chu What about some of the other risk factors in addition to genetics?

Harris As Gina has said, about 10% of women have a strong family history of breast cancer, but there are other risk factors such as the age when a woman starts to menstruate; the earlier the age the higher risk of breast cancer. The age at which she has her first pregnancy and the length of her menses, in other words how long she continues to menstruate until she goes through menopause, can be risk factors.

Chu When should women start getting mammograms, which is the gold standard for this disease?

Chung In this day and age screening mammograms are indeed still considered the gold standard, although there is some controversy, most people agree that screening should start for the typical patient at 40, and annually thereafter.

Chu And in those women who have a strong family history of breast cancer, when would you suggest they start screening?

Chung That varies, however, one of the things that we use as a rule of thumb, is certainly if you have a family member that was diagnosed with breast cancer at a very early age we say that screening for other family member should begin approximately 10 years before the age of which that patient was diagnosed. In addition to when screening should start, perhaps other screening or newer screening modalities should be considered such as breast MRIs.

Chu On that point, there has been a lot made in the press about the benefits of breast MRIs. What are your thoughts on that?

Chung MRIs are a great tool, but for use with certain patients and certain special circumstances. We are still beginning to try and understand where and when we should implement it. As a screening modality, the problem with MRIs is that they are very sensitive, perhaps more sensitive than mammograms at detecting small abnormalities; however, it may be a little too sensitive and thus the risks of false

positives are higher. At this point we try to limit use to those with the highest risk, but we are still trying to understand when to use it better.

Chu Lyndsay, what about the issue of self-breast exams? When should they begin and should women be educated and properly trained on how best to do that?

Harris Self-breast exams also represent an area of controversy. The reason is that survival has not been definitively shown to be improved by self-breast exam alone. The current understanding, or recommendation, is that it is still very important for a woman to understand the architecture of her breast. We know as oncologists that many patients detect their own breast cancers, and we also know that if done properly, a woman can detect a change before her provider can detect it. We currently recommend to all our patients that they do their breast exams after their menses, usually a week or so after, and that they get to know their breasts and do that at least on a monthly basis.

Chu And again when should that start?

Harris As soon as the women develops breasts.

Chu So that is pretty early on, in their teens?

Harris Teenagers, yes.

Chu What are some of the symptoms, or what should women look for when they do their self-breast exams? What might be a harbinger for breast cancer?

Chung Certainly in younger women they naturally tend to have what we call more lumpy breasts, so not every lump is necessarily a breast cancer. But of course, as Lyndsay mentioned, it is very important for a woman to be familiar with the way her breasts normally feel, and for younger women, how it may change throughout the menstrual cycle. Typically a breast lump is considered something that could be a harbinger for breast cancer, but there are other more subtle changes that can signal something abnormal, like changes in the way the skin looks and feels, a firmer texture, changes in the way the nipple looks, sometimes it becomes more inverted and pointing inwards and other subtle changes such as dimpling of the skin.

Chu Tenderness of the breast, should that be a cause for women to be worried?

Chung In general, breast cancer is not associated with a lot of breast pain, but for certain types of breast cancers that could be one of the findings.

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- Chu If a woman were to detect a new lump or mass, which is clearly different, what should she then do?
- Harris She should examine the breast and check it again perhaps a few days later. If it persists, she should see her family physician or her gynecologist and ask them to do a breast exam.
- Chu And if they go to the family doctor or the GYN specialist, and they confirm that there is a lump that is clearly different, what is the next step?
- Harris Every women with a suspicious breast lump should have a mammogram, typically if there is a palpable lump, if something can be felt, it should also include an ultrasound examination.
- Chu Let us walk through that whole process. The ultrasound is done, and indeed there is a mass there? What then happens?
- Harris What the specialists in breast radiology do is they look for changes on the mammogram, shadows and calcifications that may indicate the sign of malignancy. They also look for a solid lump, not a cyst, but something that is solid. If any or both of those signs are present, they would then do a biopsy.
- Chu And the biopsy is usually done by a surgeon who specializes in breast disease.
- Harris Yeah, and either the surgeon or the radiologist can do the biopsy. It is quite typical for radiology to do many of the core biopsies now-a-days because they are the first people who contact a woman who has a new breast abnormality.
- Chu One point to emphasize is that the radiology and the biopsy procedures really should be done in a coordinating fashion by a group of experts who specialize in breast disease.
- Chung I absolutely agree. Once a woman is diagnosed with breast cancer, of course the treatment approach is a multimodality approach with many different specialists involved in the management. It is important to try to get them involved as early as possible.
- Harris We have surgical breast cancer oncologists who focus only on breast cancer treatment. We have radiation oncologists who focus only on breast cancer treatment and we have medical oncologists who again, just treat breast cancer. In addition, we have pathologists, radiologists and we have experts in lab medicine who know specifically the details of breast cancer and this team comes together to provide the best approach for an individual patient with the diagnosis of breast cancer. As Gina pointed out, having a specialist who does only breast cancer as

their focus provides the optimal situation for a patient who can have a very serious health problem.

Chu We would like to remind you to email your questions to canceranswers@yale.edu or call 188-234-4YCC. At this time, we are going to take a short break for medical minute. Please stay tune to learn more information about breast cancer with our special guests, Dr. Lyndsay Harris and Dr. Gina Chung.

Medical Minute

It is estimated that over 2 million people in the US are currently living with prostate cancer. One in six American men will develop prostate cancer in the course of his lifetime, but major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who will die from this disease. Screening for prostate cancer can be performed quickly and easily in a physician's office using two simple tests, a physical exam and a blood test. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for prostate cancer. The patient's enrolled in these trials are given access to experiments and medicines not yet approved by the Food and Drug Administration. This has been a medical minute. You will find more information at yalecancercenter.org. You are listening to the WNPR health forum from Connecticut public radio.

Chu Welcome back to Yale Cancer Center Answers. This is Dr. Ed Chu and I am here in the studio this evening with my guests, Dr. Lyndsay Harris and Gina Chung, both from the Yale Cancer Center talking about the latest developments in breast cancer. Let's switch gears a little bit and talk about the treatment of breast cancer. Starting with you Gina, how do we approach the treatment of breast cancer depending upon the individual patient?

Chung The treatment of breast cancer is of course dependent on a number of factors that we call prognostic factors; most importantly, the stage of the breast cancer, basically how big the tumor is and whether there is involvement of the lymph nodes underneath the arm and if there are any distant sites of cancer in the body. This will dictate what kind of medications we would recommend to the patient and whether chemotherapy, biologic therapies, hormonal therapies, and even surgery and radiation may be offered to the patient, but in general, it is usually a combination of surgery, radiation, and medications.

Chu If a woman has breast cancer that is localized to the breasts, is it sufficient for that woman to just have surgery, plus or minus lymph node dissection, and then followed with no further treatment?

Chung In a small proportion of patients it may be, but again, to stress the importance of a

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multidisciplinary approach, now-a-days we are giving a lot of medications and radiation above and beyond just surgical resections. It is important for the patient to see specialists in other fields as well, to really understand what their risks are and to discuss the potential benefits and pros and cons of medications and radiation.

- Chu Lyndsay, one of the terms we hear about is adjuvant therapy; adjuvant chemotherapy and adjuvant hormonal therapy. How do you decide when to use that particular approach in a woman who has had surgery and needs follow-up care?
- Harris As Gina has said, many woman are now receiving medication in addition to the local therapy, surgery and radiation, and the decision is really based on those features of the patient's breast cancer, the size of the tumor, the lymph node involvement and also specific markers in the tumor itself dictate which type of therapy may be the best.
- Chu What type of markers do you look at specifically?
- Harris It is now standard of care to look at the estrogen receptor, the progesterone receptor and the HER2 receptor on every breast cancer that is diagnosed. Those markers tell us not only the behavior of the tumor, but more importantly what the best therapy for that particular patient is.
- Chu Are there any differences in the expression of those specific markers, say in Caucasian women as opposed to African-American women?
- Harris Yes, and the entire explanation for the disparity in survival between African-American women and Caucasian women is not understood, but part of the disparity may be due to the fact that they have a more aggressive type of breast cancer. It is typically what we call triple negative estrogen, progesterone and HER2 receptor negative, and those tumors tend to be more aggressive.
- Chu And obviously then the treatment strategy would be quite different in that triple negative disease.
- Harris That is right. If a woman has the estrogen receptor she is typically offered hormonal therapy such as tamoxifen and aromatase inhibitor or a drug such as that. If she has HER2, she is typically offered Herceptin as part of her adjuvant therapy or therapy after surgery. However, if she has none of those receptors we know that chemotherapy is actually more effective in patients with triple negative tumors and they are very likely to be offered chemotherapy as their adjuvant therapy of choice.

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- Chu Gina, you have been very actively involved in trying to understand the process of angiogenesis and developing treatment strategies that target that process. What is angiogenesis and what are some of the strategies that you in particular have been focusing on?
- Chung Angiogenesis is the process of blood vessel growth. In simplified forms for a tumor to grow beyond a certain size, let us say a few millimeters, the hypothesis is that it needs new blood vessel growth to supply the oxygen and nutrients to continue its growth and spread. In the laboratory, there has been a lot of research that confirms that this is a very important process in cancers and breast cancers as well. Therefore, there has been a lot of research recently looking at ways we can interrupt or inhibit this process in the hopes that we can inhibit the growth of the tumor. We have come a long way, for example, Avastin, which is an antibody similar to Herceptin but it targets a molecule called vascular endothelial growth factor or VEGF, has been shown to be effective in a variety of cancers including breast cancers and is recently approved for use in breast cancer and women with advanced breast cancer.
- Chu Which is really a very remarkable advance, certainly in the disease that I know much better, which is colorectal cancer. That is where Avastin was initially approved, but was then subsequently approved for lung cancer and just within the last couple of weeks it has been approved, as you said, for breast cancer. Now is it approved for use as a single agent or to be used in combination therapy?
- Chung The best and most optimal way of using Avastin is not entirely clear yet, but the principle study that lead to its approval was a large study in women with stage IV metastatic breast cancer who were given this treatment as a part of their treatment program as the initial treatment for their stage IV breast cancer. It involved Avastin, plus a chemotherapy, in that instance Taxol, versus just the chemotherapy Taxol alone, and it showed benefit above and beyond chemotherapy alone. We try to develop clinical trials that target multiple stages of breast cancer, but also subtypes of breast cancer, and antiangiogenic agents are a very important part of this program. For those with early-stage breast cancer, we do have a clinical trial with preoperative therapy, which is before surgery, and this involves giving Avastin plus letrozole, which is a hormonal therapy, for about 4 months before surgery. This way we can try to use a very exciting combination of medications to shrink the tumor before the patient has surgery to optimize the surgical result and also see the individual responses in the patient. For those with metastatic or stage IV breast cancers, we have several clinical trials including a drug called sorafenib, which targets different important pathways including angiogenesis pathways as well as other drugs important in the angiogenesis process.

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- Chu You are also trying to develop what we call biomarkers of response to these treatments that target angiogenesis. Can you tell us a little bit about that as well?
- Chung Fortunately, for drugs like tamoxifen, hormonal therapy and even Herceptin, we do have some measures of markers that we think can predict whether a patient will have benefit with those drugs. For example, if a woman has estrogen receptor expression, then those are the patients that usually benefit from tamoxifen and it's similar for HER2/neu expression and Herceptin. Unfortunately, for the angiogenesis agents that are currently being studied, no clear markers exist. This is very important because it allows us to tailor the therapy most appropriately. It is very important to try to develop markers both in tissue and other samples that can help guide us in deciding which patients should get these treatments. We do have several different important studies built into the clinical trials both in tissue samples as well as in blood that will hopefully allow us to better understand how these agents work and to give us markers to predict response better.
- Chu Lyndsay, you have also been very actively involved in developing clinical trials.
- Harris What we tried to do in the breast program is to provide clinical trials for women at all stages of breast cancer and also different subtypes of breast cancer. We have a portfolio of clinical trials that address the HER2 positive type of breast cancer. We have a group that targets the estrogen receptor positive group of breast cancer and then we have a set of trials that target triple negative breast cancer. We have specific trials that address each of those different subgroups of breast cancer. Gina's entire program, which is an angiogenesis based program, actually crosses boundaries because it is effective in several different subtypes, but we want to explore all different options for patients because we do not know at this point what is going to be the best strategy for women with breast cancer.
- Chu I understand you are the principal investigator of a large cooperative group study that is being conducted called the ALTO trial.
- Harris Yes, in the HER2 subgroup of breast cancer, we have several clinical trials that focus on HER2 in the metastatic setting after Herceptin and Tykerb have no longer continued to be effective. We have a couple of trials that look at other options for those patients including the drug rapamycin. In the early stage setting, we have two preoperative trials that look at new drugs for HER2 breast cancer, which include Tykerb or lapatinib. We also have an opportunity in the adjuvant setting, the ALTO trial, which has just been launched, which is a collaboration between Europe, the United States and Canada. That trial is for HER2 positive breast cancer patients who have completed their local therapy. In the trial they would receive either Herceptin or the drug lapatinib or Tykerb, which is the same drug just with a different name, or a combination of the two. That trial is to see what the optimal targeted therapy for HER2 positive breast cancer patients is.

Chu What is great to see is that just within the last 3 to 5 years, we have seen tremendous advances in the treatment of breast cancer and it has become very individualized as to how we develop these treatment strategies.

Harris I completely agree with you. Having been in the field for about 15 to 20 years, I am gratified by the progress that we have made in the improvement of survival, which I think is largely due to targeted therapies.

Chu Gina and Lyndsay, it has been great having you. It is amazing how fast time has gone and we are at the end of the show. Thank you so much for joining me this evening on Yale Cancer Center Answers. Until next week, this is Dr. Ed Chu from the Yale Cancer Center wishing you a safe and healthy week.

If you have questions, comments, or would like to subscribe to our podcast, go to yalecancercenter.org where you will also find transcripts of past broadcasts in written form. Next week, you will meet Dr. Fred Okuku, a fellow in medical oncology from Uganda.