

Welcome to Yale Cancer Center Answers with doctors Francine Foss and Lynn Wilson. I am Bruce Barber. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This evening Lynn Wilson welcomes Dr. Erin Hofstatter. Dr. Hofstatter is Assistant Professor of Medicine and Medical Oncology at Yale School of Medicine and she joins us this evening for a conversation about high risk genetics and breast cancer. Here is Dr. Lynn Wilson. Wilson Let us start off by having you tell us a little bit about what high risk genetics are? Hofstatter High risk genetics is a field of medical oncology, and my specific interest is in breast oncology that identifies people who are at high risk for developing cancer over their lifetime. Wilson Tell us a little bit about your own background, and your specialized training in this area? Hofstatter Actually I grew up here in Connecticut and after I went to Amherst College I attended medical school here at the University of Connecticut. I then went to Boston for a few years and completed my training there, most recently my fellowship at Beth Israel Deaconess Medical Center in Boston. So now in a way I have come back home to Connecticut and have recently started at Yale Cancer Center as a breast oncologist. My specific interest in medical oncology started in medical school during the classes I took as a second year student, and those interests really were confirmed over the years as I saw more patients, and it confirmed my interest in pursuing a career treating patients with cancer. During my hematology/oncology fellowship, I enjoyed my interactions with all of the patients that I saw. But I was drawn to those patients being treated for breast cancer; I was most emotionally connected with those patients with breast cancer. That is where that interest was developed, and then specifically, my interest in genetics came largely from a clinical rotation I did with one of my mentors, Dr. Nadine Tung at Beth Israel, as well as some of the research projects that I did both with Dr. Tung as well as Dr. Gerburg Wulf at Beth Israel. Wilson How did you develop the expertise in genetics? Obviously it sounds like the interest started there, but did you do additional course work or research? How did that come about, how do you get to the point where you have expertise in something that is sort of a subspecialization of a subspecialization? Hofstatter A lot of that was clinically developed, unfortunately they are short of doing an additional genetics fellowship. There is not a lot of formal training in high risk genetics. So once I identified this interest, a lot of this was gathered during my clinical training. I was in a medical oncology fellowship, so I was able to focus on that during my fellowship in terms of clinical rotations, research projects, a lot of reading, a lot of rotating with different folks. Wilson I was going to say, it sounds like you have got enough responsibility during your standard training program, but to develop this additional expertise, you did a lot of extra work. Hofstatter Yes. Wilson And it was on the side at the same time? Hofstatter Yes. Wilson Tell our listeners a little about some of the genetic mutations you are interested in, concerned about, or

that you look for in a patient with breast cancer?Hofstatter Let me start by saying that most breast cancer is not genetic. In fact, about 75% of breast cancers happen just because they happen; there are not any identifiable risk factors. There is not an identifiable family history, they just happen. Again, that is about 75% of breast cancers. Only about 10% of all breast cancers can be attributed specifically to an inherited gene. In terms of that 10% of breast cancer, only about 5% of breast cancers overall can be attributed to two specific genes, namely BRCA1 and BRCA2. Those are the two gene mutations that are most commonly associated with breast cancer and, again, account for only about 5% of all breast cancers that are diagnosed each year.Wilson Although that is a small percentage, I take it that one of the reasons we try to identify the patients who have these genetic linkages is because it may have some sort of impact on their therapy, for example?Hofstatter For those women diagnosed with breast cancer, there is research going on right now for specific medications, namely PARP inhibitors. This is a specific chemotherapy that is being studied for use in those women who have been diagnosed with breast cancer who also carry a gene mutation. One of the things that is important about identifying when the cancer is related to a gene mutation is that it potentially affects a woman's choice about her surgical options for the treatment of the breast, but it also impacts other cancer risks. For example, when a woman inherits a BRCA1 or 2 mutation, not only does she have increased risk for breast cancer, but she is also at and increased risk for ovarian cancer as well. More specifically, when a woman inherits a gene mutation, a BRCA1 or 2 mutation, her lifetime risk of developing breast cancer is upwards of 85%, and in terms of ovarian cancer, her lifetime risk is upwards of 40%. So these risks are high. Certainly we take that information into consideration for treatment of her breast cancer, but we also think about ovarian cancer as well.Wilson Are there other factors that would lead you to feel that a patient may be at high risk to develop a breast cancer or one of these other cancers, or are we just talking about BRCA1 and 2? Are there other factors that you add into the determination of what constitutes high risk?6:16 into the programHofstatter Absolutely, certainly the genetic mutations are the most concerning in terms of risk of developing a breast cancer, but there are other groups of high risk women. For example, if a woman has received radiation therapy to her chest, perhaps for Hodgkin's disease in the past, something like that. Other women who might be at high risk include those who have been diagnosed on surgical biopsy with high risk features, specifically atypical ductal hyperplasia, or what is called LCIS or lobular carcinoma in situ. These are diagnoses that we wouldn't know about unless a woman underwent a breast biopsy for another reason, perhaps something was found on a mammogram, and then lastly, you could argue that there are women that have a strong family history of breast cancer, but have not been found to have a gene mutation. They are also at increased risk of breast cancer. Certainly, family history with multiple generations affected by breast cancer, young breast cancers, these are red flags for either a gene mutation that we can identify or perhaps not identify. We do feel strongly that there are a number of genes out there that can be passed along that we just are smart enough to identify quite

yet. Wilson What sort of recommendations do you have for a patient who has a strong family history, for example, say there is a patient who seems fine right now, not having any problems, but has a sister who had breast cancer, a mother, and a grandmother who had breast cancer. What are some of the guidelines in terms of risks assessment, genetic testing, at what age, and what groups of patients should be considered for this? Hofstatter This is a great question and is an important question to answer. Let me begin by saying the most informative person in the family to test for a gene mutation would be the person who is effected with cancer themselves. That would give the most informative results that you can get that would certainly tell you whether or not that persons cancer could potentially be related to a BRCA1 or 2 mutation, or another gene mutation that we could look for. In terms of red flags, sometimes it is not possible to test the person with cancer. So, family histories that would have red flags would certainly be if there is a known mutation in the family, but otherwise breast cancers that are diagnosed at a young age, 45 or younger, certainly should be considered for testing, certainly if there are multiple breast cancers in the family. Particularly if one of those breast cancers is at age 50 or younger. If you are looking at multiple generations, or multiple people within the generation that are affected that would be a red flag. Ovarian cancer in the family at any age, particularly if it is in combination with breast cancer, is a big red flag for consideration of genetic testing. Male breast cancer in the family is a red flag, and there are particular populations of people who are at higher risk of carrying mutations, specifically those of Ashkenazi Jewish ethnicity. In the general US population, the frequency of having a gene mutation of BRCA1 or 2 is about 1 in 400 people. However, in the Ashkenazi Jewish population, that frequency is about 1 in 40. Automatically those folks are at higher risk for carrying a gene mutation. Therefore, if you are of Ashkenazi Jewish heritage and you have a breast cancer, you should be tested. Wilson How do we actually do the test? 9:39 into the program Hofstatter It is a blood test that is done, but it is not that easy. The recommendations are that folks obtain this test at the referral of their doctor to a cancer genetic counselor, and we have got a terrific program here at Yale run by Ellen Matloff specifically for cancer genetic counseling. Often times a patient will either call on their own because they are concerned, or more often they are referred by a doctor for counseling. During that counseling, the counselors are able to sit with the patient and go through their family history in great detail, assess what their risk is, and whether or not the risk is high enough to go ahead and send the test. Then the patient returns for their results so they can discuss in detail the implication of the results, and how to interpret the results, because like any test there are positives, negatives, and grey area. Wilson It is complicated. It is not like coming in and just getting a blood count and the doctor tells you it is normal and you are all set to go after that. Hofstatter Exactly. And what is concerning is that there are increasing commercials and marketing for folks to send off a cheek swab, if you will, basically you take Q-tip and swab the inside of your mouth and mail it off to the company to tell you what your DNA test shows. That is concerning to us because sometimes, like I just mentioned, the results can be difficult

to interpret. Our concern is that when folks undergo genetic testing without specific counseling, errors can occur. Wilson I am sure in some cases there may be some results that perhaps are considered abnormal, which the patient could get a lot of anxiety about, but explained through a professional, it may not be as concerning as one might think just by looking at a piece of paper. Hofstatter Absolutely. Wilson This is important. We have talked about your expertise and interest in genetics, tell us a little bit more about your active role in the breast cancer program. What your week is like, for example? Hofstatter I would say that my role within the breast cancer program is three fold. Primarily I am there to provide clinical care to the patients, both for women who are affected with breast cancer as well as those women who are at high risk of developing breast cancer, but do not yet have the disease. A component of my job is involvement with clinical research and I also provide medical education to medical students, residents, and fellows. Wilson What are some of the challenges that you face working with women who have not been diagnosed with breast cancer, but you think may be at risk based on some of the things you have already discussed with us? Hofstatter I would say the biggest challenge really is dealing with the uncertainty of whether or not these particular patients are going to go on to develop the disease. On the one hand you want to do as much as you can to prevent cancer from occurring, but certainly not at the cost of causing potential side effects or causing a person to go through a significant procedure when you are not even sure that a cancer is definitely going to develop, and quite frankly these are otherwise healthy people who do not have cancer. It really is a balance between trying to be as aggressive as you can and not causing any unnecessary side effects or potentially even harm. Wilson How do you do that? Do you see them on a more frequent clinical basis? Is there certain testing you recommend? What would be different for a patient in follow-up who is at high risk compared to a patient who is not at high risk, who might be seeing a physician once a year for a general evaluation and perhaps get an annual mammogram, for example? What is different about the high risk patient in terms of what they may have to go through as far as what you would recommend? Hofstatter One of the things that we would recommend is more frequent breast exams. A clinical exam every six months is usually standard of care for folks at high risk. Either the folks are coming to me to follow them for high risk surveillance or this can be completed by the person's primary care physician or gynecologist. So long as the physician is examining them every six months. Certainly annual mammogram plays a big role in surveillance, but another question would be what could the role potentially be for breast ultrasound, or more specifically, breast MRI for these women? There is a certain group of high-risk women, those who are felt to have greater than a 20% lifetime risk of developing breast cancer that would qualify for an annual breast MRI. For many of my patients, I am following them both with an annual mammogram as well as annual breast MRI. Wilson We are going to take a short break for a medical minute. Please stay tuned to learn more information about high risk genetics with Dr. Erin Hofstatter. Medical Minute The American Cancer Society estimates that last year there were over 65,000 new

cases of melanoma in this country and over a thousand patients were diagnosed annually in Connecticut alone. While melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths. Early detection is the key. When detected early, melanoma is easily treated and highly curable and new treatment options and surgical techniques are giving melanoma survivors more hope than they have ever had before. Clinical trials are currently underway at Yale Cancer Center, Connecticut's federally designated comprehensive cancer center to test innovative new treatments for melanoma. The specialized programs of research excellence in skin cancer grant at Yale, also known as the SPORC Grant, will help establish national guidelines on modifying behavior and on prevention as well as identification of new drug targets. This has been a medical minute brought to you as a public service by Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network. Wilson Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson and I am joined by Dr. Erin Hofstatter and we were discussing high risk genetics and breast cancer. Erin, before the break 15:39 into the program you talked a little bit about the clinical follow-up program for patients who might be or have been identified as being at high risk, and you mentioned mammogram, talk to our listeners about what a mammogram does, what is involved, and some of the other procedures such as ultrasound, MRI, and these diagnostic tests. Hofstatter There were three that I mentioned earlier in terms of standard breast imaging to screen for breast cancers. I think the one that most people are familiar with is the annual mammogram that women undergo usually starting at age 40 and onwards. I think many of the women in the audience are familiar with mammogram which basically uses x-rays, special x-rays taken of the breast when the breast is compressed so that the best possible imaging can be obtained. Mammogram is very good at picking up cancers, and if you have been paying any attention to the news, there has been a lot of news about mammogram and whether it is good and whether it should be done in young woman or not. I think that we as breast oncologists do continue to recommend that mammogram start at age 40 and continue annually from there. Obviously this needs to be discussed with a woman's doctor, but as of right now that is consistent with the American Cancer Society's recommendations and that is what I would advocate for. Wilson And for someone who is not at high risk? Hofstatter I would say for the average American women, I would recommend starting at age 40. Certainly women who are at higher risk should start at an earlier age, potentially even as early as 30. As I mentioned, mammogram is very good at picking up breast cancers, but cannot pick up all breast cancers and that is where we start looking for other imaging such as ultrasound or potentially breast MRI. Many women who are receiving their mammogram reports now in the state of Connecticut are receiving information about the possibility of dense breast tissue. On the bottom of many of the mammogram reports there is a statement that you may have dense breast tissue, you should talk with your doctor about considering ultrasound. The reason for that is because mammogram is essentially an x-ray and dense breast tissue shows up

as white on the mammogram. However, cancer shows up as white on the mammogram. So, it is very difficult to pick out a white cancer on the background of white breast tissue. What that basically means is when there is a statement about dense breast tissue the woman's mammogram may not be as effective at picking up a breast cancer. That is when we start thinking about using either breast ultrasound or breast MRI to look for these breast cancers. Ultrasound is an easy painless procedure using basically a hand held probe. You put a little gel on the women's skin and you pull the probe over the skin and you examine the breast for any other additional findings. Often times this works well in conjunction with mammogram for picking up other lesions that the mammogram might miss. But what is better for adjunct screening really, is breast MRI. This is a very sensitive radiographic technique to find breast cancers. Often times the woman is lying on her stomach and the breast is imaged. The MRI does take longer than a mammogram, though I am told it is not as uncomfortable potentially as a mammogram. The difficulty with breast MRI, however, is that it is very sensitive, which on the one hand is good because it will pick up many more breast cancers, but the downside is that it is very very sensitive so you have a much higher chance of having a false positive result with breast MRI. This could potentially lead to increased anxiety on the part of the woman who is told that her breast MRI is abnormal, it could potentially lead to biopsy and that can become a problem particularly if a woman has a breast MRI that continues to have false positives. Again, the sensitivity of the breast MRI can be a double-edged sword sometimes. Wilson You talked a little bit about the real importance of counseling for patients who not only are at high risk, but anybody getting a genetic based test. The counseling is a key feature to interpret the results whether they are abnormal or normal. Are there other things that are offered to women who are at high risk, such as clinical trials, are there research investigations going on so that we can learn more about patients who are at high risk? Hofstatter Absolutely. I would say that the area of research within breast cancer treatment, breast cancer prevention, and breast cancer genetics is abundant. Specifically, in terms of the gene mutations that I mentioned, BRCA1 and BRCA2 are the most commonly known, but there are a lot that we still do not understand even about those gene mutations. For example, we do not exactly understand why they appear to behave differently in different people, even within the same family. For example, if one woman has inherited a BRCA2 mutation, she may develop breast cancer at age 40, whereas someone else in her family with the same exact mutation may develop breast cancer at age 60. We still do not fully understand why these mutations behave differently in different people. That is one area of research. Another important area of research is the search for additional genes that we have not discovered yet. Very often in my clinic, I see patients with an extremely strong family history of both breast and ovarian cancer, but they tested negative for BRCA1 and BRCA2 gene mutations, so it is clear to me that there is a gene running through their family, I just cannot tell them which one. So that too is an area of research. Wilson I see, so we are trying to learn more about the genes we know about and we are still trying to

figure out what causes these mutations, and we are trying to learn as much as we can. Obviously, it is complicated and multifactorial and there could be a whole array of other genes out there that we just do not know what they are yet. Hofstadter There is. In fact, another interesting area of research is that we know that there are a number of what are considered low-risk breast cancer genes out there, in fact, they are quite common in the population. One of these low-risk gene mutations itself does not cause breast cancer, but if you started inheriting five of these, ten of these, twenty of these low-risk genes, we are starting to wonder if potentially a combination of some of these low-risk genes may translate to an outcome of breast cancer. So, that is another important area of research that is being pursued right now as well. Wilson We all have genes as a part of our genetic makeup. Explain to our listeners what is meant by a mutation? What is that? 22:38 into the program Hofstadter A mutation is basically an abnormality in the DNA and I am glad you asked that question. We have talked a lot about BRCA1 and BRCA2 and looking for these genes, in fact, we all have these genes. Everybody has BRCA1 genes and everybody has BRCA2 genes. It is when these genes are mutated or are incorrect, broken if you will, is when problems begin. When a person inherits a BRCA1 or BRCA2 mutation, they are basically inheriting a broken copy of these genes. These genes are important in the normal person because they work to repair DNA and many people are surprised to know that DNA gets broken all the time, but we have been designed to repair the DNA naturally. However, when somebody inherits a broken copy of BRCA1 or BRCA2, fortunately they have a backup copy that can work to repair the DNA. Unfortunately, in many of these folks who inherit a mutation the second copy, or the backup copy, breaks as well and that is what causes the setup for cancer when you have two broken copies of these DNA repair genes. Wilson If we have a woman who has these mutations, what sort of things can you speak to her about regarding reduction of her risks going forward in terms of trials, medications, and surgical procedures? Talk to the listeners about what is available. We do the counseling, we've got the information, the patient understands what is going on, what can we do proactively moving forward to help reduce risk of a bad outcome? Hofstadter There are three main areas that I talk to my patients about in terms of reducing their risk of breast cancer. The first is what surgical option the patient has, and what I am specifically talking about there is whether or not a woman should consider undergoing a double mastectomy or basically removal of the breast tissue on both sides. This is a very effective way of reducing the risks of breast cancer, in fact, there have been studies that show in woman who are gene mutations carriers, they can reduce their risks of developing breast cancer by 90% or more. We cannot do anything to make the risk zero, but certainly prophylactic mastectomies or removal of the breast is the most effective way to prevent breast cancer from happening in the first place. Usually this is an extreme, this is the most aggressive thing that you can do to prevent breast cancer and I would say most times, the women considering this procedure are those women with identified gene mutations, or perhaps those woman with LCIS, or lobular carcinoma in situ. But it remains an option for other women who, again, appear to have a

very very strong family history of breast cancer. So that would be something to consider in terms of reduction of breast cancer. I also mentioned earlier the possibility of removal of the ovaries in women who are BRCA1 or BRCA2 gene mutation carriers, because again this translates to a risk of developing ovarian cancer as well. By removing their ovaries, not only does that reduce the risk of ovarian cancer, but actually if it is done in a perimenopausal woman, a woman who is still menstruating, it can actually reduce her risk of breast cancer as well. So the benefit is two-fold there.

Wilson Is that because of the changes in the hormonal makeup of the body?

Hofstatter It is. It is basically taking away a substantial amount of the women's estrogen in her body and it is felt that elevated levels of estrogen are related to the development of breast cancer. So, surgery is certainly something I talk about with women. The second area that I talk about with women is if26:26 into the program

there is a medication that they can use to prevent or lower the risk of breast cancer, and there are two that are FDA approved, tamoxifen and raloxifene, otherwise known as Evista. Of the two, tamoxifen, I would say is the better known. Evista is an osteoporosis medication that in hindsight they found also prevented breast cancer. However, these medications, while effective, they can reduce the risk of breast cancer by approximately half, they do have side effects and that is where you have to start weighing the pros and cons of using these medications. The good things are that they do help your bones and they prevent breast cancer, but the downside is they have side effects such as hot flashes, night sweats, risk of blood clots, risk of stroke, and tamoxifen additionally has a very small risk of causing uterine cancer. Certainly when you are considering using these medications in otherwise healthy people who do not yet have breast cancer and may never have breast cancer, you have to begin to weigh the pros and cons of how much risk there is of breast cancer versus how much risk there is of side effects.

Wilson With tamoxifen, for example, when that is used therapeutically for a woman who has had a diagnosis of breast cancer and has been treated, we typically recommend tamoxifen for say five years. Is the recommendation for someone who is at higher risk where we are using tamoxifen, is it known how long we should use that medication for? Do the same types of rules apply or do we not really know?

Hofstatter That is a good question. Studies that have been done comparing tamoxifen to placebo, or basically a sugar pill, and the studies that have been done comparing tamoxifen directly with Evista, both used regimens that were one pill a day for five years; similar to how tamoxifen is used for breast cancer. It has also been proven that the protective effects of using these medications last even beyond the years that they are taken, for tamoxifen in particular, the 10-year follow-up data shows that protective affect last at least 10 years, if not longer. We will continue to get this data as time goes on.

Wilson Tell us a little bit about what you see developing in your program in the future.

Hofstatter We will be opening up a number of clinical trials here at Yale in the coming years. Specifically looking at different markers for breast cancer risk, looking at a diabetes medications, specifically metformin, as a potential risk reduction agent in women at high risk of breast cancer as well as some other medications that we have identified for folks who have been di-

agnosed with things such as atypical ductal hyperplasia, other specific high-risk women. I would say globally there is great potential for research going forward, specifically for chemoprevention, surgical prevention and a better understanding of the genes. I think long term the hope is that once we have a better understanding of what genes are causing the breast cancer, and how these genes may be playing out in each individual, we will be able to tailor our prevention strategies for these women so that we can effectively prevent breast cancer from happening in the first place. Dr. Erin Hofstatter is Assistant Professor of Medicine in Medical Oncology at Yale School of Medicine. If you have questions or would like to share your comments, visit yalecancercenter.org, where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.