Dr. Michael DiGiovanna, Coping with a Breast Cancer Diagnosis May 30, 2010Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of 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 1888-234-4YCC. This evening Ed and Francine welcome Dr. Michael DiGiovanna. Dr. DiGiovanna is an Associate Professor of Medical Oncology at Yale School of Medicine and Yale Cancer Center, specializing in the treatment of breast cancer. Here is Ed Chu.Chu Why don't we start off by first defining what breast cancer is and then maybe you can share with us how common and how significant a problem breast cancer is?DiGiovanna The breast is basically an organ that is designed to produce milk for a baby, and coming from the nipples are a series of ducts called the milk ducts and at the end of the milk ducts are little grape like structures that are called lobules. When a woman is breastfeeding, the milk is made in the lobules and flows out to the baby through the ducts, as if the ducts are straws. And so what breast cancer is, is cancer that arises in those cells that are lining the ducts or the lobules and that's why anyone familiar with breast cancer might know that the two main types of breast cancer are ductal cancer or lobular cancer. About 85% of cancer is ductal cancer and the other 15% is lobular cancer. And in terms of how frequent breast cancer is, it's an extremely common disease. The number one risk factor is considered just being female because there are no women who are not at risk of breast cancer. It's a very common disease and in the United States at this time almost one out of eight women will be diagnosed with breast cancer statistically sometime in their lifetime.Foss Mike, we used to say one in nine and now you are saying one in eight, so that suggests to me that the incidence overall is increasing.DiGiovanna The incidence has actually been slowly and steadily increasing now for actually most of the last century, and there are some clues as to why those reasons might be, but despite the fact that the incidence has been increasing, the death rate for most of the last century has remained flat and finally since about the 1990s, the death rate has actually been going down.Foss That's one good thing about our War on Cancer, we are actually winning in one arena.DiGiovanna We are winning in breast cancer for sure.Chu And maybe we can get to why we are winning in a little bit, but just to go back to some of the basics, other than being a woman, what are some of the other key risk factors?2:55 into mp3 file http://yalecancercenter.org/podcast/may3110-cancer-answers-DiGiovanna.mp3DiGiovanna One of the most important risk factors is if there is a family history of breast cancer, because the tendency to develop breast cancer can be genetically inherited and run in families. But what is important to point out and what a lot of people don't realize is that most of the time that's not the case, only about 5% or 10% of the time does it run in families and the other 90% is random or sporadic.Foss Is there a racial predilection for breast cancer?DiGiovanna There is. In the United

States, the highest prevalence is in Caucasian woman with a little less so in African-Americans, and interestingly, Asians have among the lowest rates of breast cancer. However, Asians who migrate and live in the United States have a higher rate than Asians who remain in their native countries, but not as high as the Caucasian and African-Americans in our country.Chu When does breast cancer typically present in terms of age?DiGiovanna The average age is about 60 in the United States, and that raises the question, since we were talking about the genetic background, that one of the clues that a family might have a genetically inherited type of breast cancer is when it strikes at an usually young age, for example in the 30s or the 40s.Foss Does breast cancer ever occur in very young women in their teens or twenties?DiGiovanna It can very occasionally occur in the 20s. At Yale, the youngest patient that we have had has been 18 years old. I have not seen or heard of any younger than that, it's even exceptionally rare in the 20s, but we do have some patients in their 20s as well.Chu When we talk about family history, which presumably could increase the risk for developing breast cancer, do you only look at the mom's side or do you also have to look at the dad's side?DiGiovanna It's important to look at both the mother's side and the father's side because the tendency of genetics is that it can come from either side of the family. Those 5% or 10% of families in which breast cancer seems to be genetic, we have identified two genes that account for about half of those families and those genes are called BRCA1 and BRCA2. It stands for breast cancer gene 1 and breast cancer gene 2. But it's interesting that you brought up the males and the paternal half of the family because these genes can also cause breast cancer in men and seem to be associated with prostate cancer in men as well. Men of course can pass on these genes to their offspring and make the offspring at risk for breast or ovarian cancer.5:37 into mp3 file http://yalecancercenter.org/podcast/may3110-cancer-answers-DiGiovanna.mp3Foss When you see a new patient with breast cancer how important is it for you to obtain these genes and do essential genetic testing on these women?DiGiovanna We take a very careful family history and the odds of carrying a gene, BRCA1 or BRCA2, factor into whether we will recommend referral for genetic testing for these genes. The likelihood of carrying one of these two genes rises the more cases of breast cancer in the family, in what we call first-degree-relatives, a person's mother, sister or daughter. It rises also if there is both breast cancer and ovarian cancer in the family because these genes cause both of those types of cancer. The risk rises also, as I have said, if there are unusually early ages of diagnosis in the family and we actually consider 45 or younger an unusually early age, such that even without any family history at all someone diagnosed 45 or younger, we will refer for genetic testing. The other risk factor for carrying one of these genes is being of Ashkenazi Jewish ancestry. In the United States, approximately one out of 41 or 42 Ashkenazi Jewish people carry a mutation in one of these genes.Foss Is the frequency of mutations in these genes the same for Caucasians as well as other ethnic groups, or are there specific groups that have a higher risk other than the Ashkenazi's?DiGiovanna The Ashkenazi's have by far the highest risk, but there are some other pockets

as well including a group in Iceland that has a particularly high frequency of one of these mutations.Chu But again, if one has a mutation in say the BRCA1 and BRCA2, what would be the potential risk for that individual developing breast cancer?DiGiovanna The risk of developing breast cancer is as high as about 50% to 85% sometime in their life, so much higher than 1 out of 8 for the average women and the risk of developing ovarian cancer is on the order of about 35% to 50%, and that's in a sense the more worrisome cancer because we do have effective screening for breast cancer to catch it early, but we don't have effective screening for ovarian cancer.Foss For those particular families who undergo genetic testing, would all of the screening procedures start at a very young age?DiGiovanna Yes, in fact, if we know somebody is a carrier we will recommend those women begin having mammograms and even potentially MRIs of the breast in addition to mammograms starting at age 25 as opposed to the general population where we recommend starting at age 40.Chu You have hit on the topic of screening and early detection. So for average risk individuals who don't have a strong family history, who don't have these underlying genetic abnormalities, when would the screening usually begin?8:29 into mp3 file http://yalecancercenter.org/podcast/may3110-cancer-answers-DiGiovanna.mp3 DiGiovanna We would recommend having annual mammograms beginning at age 40 and we recommend that all adult women do monthly self-breast examinations looking for lumps or any other changes in the breasts. For young women we recommend that that be performed once a month after the menstrual period has been completed because in the premenstrual time the breasts tend to be lumpier and tender. We also recommend that all adult women when they have general physical examinations from their physicians that they have the physician conduct a breast exam as well.Chu There has been a lot in the news and literature about the potential role of MRIs as opposed to screening mammograms, what are your thoughts on that subject?DiGiovanna MRIs actually seem to be even more sensitive than mammograms. The biggest downside of MRIs is that they are too sensitive. They have what we call a lot of false positives, meaning a lot of things show up on them that we are not sure what they are and usually turn out not to be cancer. We don't routinely recommend that all women have screening with MRIs because if we did recommend that to all women it would probably be a line going down the sidewalk for biopsies. However, we do recommend it for the women at the highest risk of breast cancer and the most well-defined group in that sense is those who do carry mutation in BRCA1 or BRCA2. So for those women, the recommendation is an annual mammogram and MRI.Foss Mike, can you take us down the road say of a woman who goes in and has a screening mammogram and something is seen that's abnormal, what happens next?DiGiovanna The important thing for most women to realize is that most abnormal mammograms turn out to be not cancer, but we want to err on the side of being overcautious and act on any finding. And so if there is an abnormality on the mammogram, there are different degrees of how suspicious it might look to the radiologist reading the mammogram, and if it looks probably benign, the mammographer might simply recommend an earlier than usual mammogram. So, perhaps

return in six months rather than waiting a year, so that it can be monitored a little more closely. The mammographer also might simply recommend coming in for additional views, additional pictures to make sure the abnormality was really there or perhaps just a shadow, and then if it looks suspicious enough, the mammographer would then of course recommend a biopsy.Chu Mike, what would be the findings on the screening mammogram that would increase, or elevate, the level of suspicion for something untoward?DiGiovanna Probably the most common finding on a mammogram is what's called calcifications, small little tiny deposits of calcium, kind of like chalk, but even with calcifications there are suspicious looking calcifications versus benign looking calcifications. Large scattered calcifications tend to be benign and the kind that are called clusters of microcalcifications, so a little spot where there is 11:35 into mp3 file http://yalecancercenter.org/podcast/may3110-cancer-answers-DiGiovanna.mp3 one cluster of calcifications and they are very tiny with all different shapes, what we call pleomorphic, are the more suspicious calcifications. The other thing that a mammographer can see on a mammogram is a density, shadow, or marble and again they can have different degrees of how suspicious that is. If it looks like it has a nice round circle around the edges of it, it's likely to be a benign growth or fibroadenoma or a benign lymph node, but on the other hand if it's hard to see the edges and it's a very irregular shape, that's more consistent with possibly being a cancer.Foss If a woman has to undergo a biopsy, what is that procedure like?DiGiovanna Now-a-days, the most common way that we do a biopsy is simply with a needle initially so that we can establish the diagnosis and then once we have the diagnosis of cancer or not cancer, then we make plans for the treatment that will come after that. Most commonly it's what's called a core needle biopsy. If it's a lump that somebody can feel, then a doctor can simply stick the needle into the lump, but if it's something that you can't feel by exam, but it's found on a mammogram, then we use a mammographically-guided needle biopsy.Chu Who would typically do that biopsy? Would it be the mammographer, radiologist, or the breast surgeon?DiGiovanna If it's a lump that you can feel on exam, it would typically be a surgeon, and if it's something that can only be seen on a mammogram, then its actually the mammographer who will bring the patient back to the mammography suite and using a mammogram guide where to poke the needle in.Foss At what point does a women need to see a breast surgeon?DiGiovanna Typically a women needs to see a breast surgeon, obviously if a biopsy comes back as cancer or if it comes back inconclusive that area has to be removed surgically to be sure of what the diagnosis is.Foss When we come back from the break, we are going to talk a little bit more about the treatment of breast cancer. You are here listening to Dr. Michael DiGiovanna talking to us today about breast cancer.14:06 into mp3 file http://yalecancercenter.org/podcast/may3110-cancer-answers-DiGiovanna.mp3using 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 da Vinci Surgical System is an option available for

patients at Yale that uses three-dimensional imaging to enable the surgeon to perform a prostatectomy without the need for a large incision. This has been a medical minute and more information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am here with my co-host Dr. Ed Chu. Today our guest is Dr. Michael DiGiovanna who joins us to discuss the treatment of breast cancer. We talked a lot about screening and identification of breast cancer at the beginning of the show Mike, could you launch us into a discussion now of what happens next, once cancer is diagnosed in a woman?DiGiovanna Once the cancer is diagnosed there is typically a team of doctors to treat breast cancer, and the three most prominent, front line members of that team are the surgeon, the medical oncologist and the radiation doctor. Breast cancer is often treated with some combination of those three modalities; surgery, radiation treatment, and medical therapy. Surgery in the old days was typically a mastectomy; now-a-days many women can have the option of having a lumpectomy rather than a mastectomy. When a lumpectomy is performed, it's standard to always give radiation to the breast and even sometimes when a mastectomy is performed we do radiation as well, although most of the time not, and then after the surgery and with the planning of the radiation we also decide if a patient needs what's called adjuvant systemic therapy, which means some kind of medicine administered by the medical oncologist with the goal of preventing a relapse in the future. As part of this multidisciplinary team there are also the doctors that are more 'behind the scenes' such as the pathologist and the mammographer or the radiologist who might read the mammograms, MRIs, or any other type of scans as well as other members of our team including social workers, nurses, and if they are going to be treated as a part of research, a research team as well. So it's very important for all of these doctors to sit down together and review the entire case to plan the strategy of the treatment.Chu Can you expand a little bit on the critical role of the pathologist? As we now know breast cancer has many different types and for that the pathologist plays the key role.DiGiovanna Right, and some ways in which the pathologist plays a role is in helping us to decide particularly what types of medical treatment or adjuvant treatment that the medical oncologist gives. Some of the ways in which we even decide in the first place whether a patient needs any adjuvant therapy comes from the pathologists report and that might include things like the size of the tumor, how many lymph nodes have had tumor spread into them, and what is the grade of the tumor, meaning17:26 into mp3 file http://yalecancercenter.org/podcast/may3110-cancer-answers-DiGiovanna.mp3 how abnormal does it look under the microscope. We also now know that there are different types of breast cancer; it's not all the same and they are treated quite differently. The pathologist does a series of tests on the tumor to look for different proteins that we call receptors, and for over100 years now, we have known that the estrogen receptor is important in breast cancer. Estrogen is the female sex hormone and there is a relationship between estrogen and breast cancer and about 60% of breast cancers are driven

by estrogen and require estrogen to grow. We call those the estrogen receptor positive types of breast cancer, or ER positive to abbreviate it, and those women will be treated with anti-estrogen pills of some sort, and for about the last 15 years we have identified another type of breast cancer that overproduces another type of receptor called HER2, and that we call the HER2 positive type of breast cancer. There is now a very effective therapy that is specifically targeted towards the HER2 protein and we do use it for the HER2 positive breast tumors. These are critical results from the pathologist, is this an estrogen receptor positive tumor or a progesterone receptive positive tumor, which is another hormone receptor indicating that they can be treated with anti-estrogen pills, or is this a HER2 type of cancer which is treated with the medications directed towards HER2, or is the type of cancer that does not have any of those in which chemotherapy is the conventional treatment if any is needed?Foss There are also cancers called intraductal cancers that may or may not require additional treatment, can you talk about those?DiGiovanna That's right. When breast cancer is caught at the very-very earliest stages, I talked about how breast cancer is really a cancer of the milk ducts or the lobules, and when you catch it very early its possible that those cancerous cells are totally confined to the inside of the milk ducts or the inside of the lobule, and that can be treated with nearly 100% cure rate because by definition there is no chance that the cancer could have spread, and it's actually the spread of cancer that makes it life threatening and so we called those the intraductal types of cancer and/or the intralobular types of cancer.Chu Do all breast cancers express this HER2 new growth factor receptor?DiGiovanna No, it's about 20% to 25% of cancers that are the HER2 positive type and about 60% are the estrogen receptor or ER positive type and some might have both ER and HER2 and some might have neither of those.Foss Back when Ed and I trained at the National Cancer Institute, we actually didn't know about HER2 and that's come along recently, now that we have got the antibody that's directed against that protein. To what degree do you think that's actually changed the treatment of breast cancer?Chu Well one of the most important breakthroughs in the treatment of breast cancer is the type of drugs20:29 into mp3 file http://yalecancercenter.org/podcast/may3110-cancer-answers-DiGiovanna.mp3 that can be used to treat HER2 positive breast cancer. We learned in the late 1980s that those HER2 positive cancers are actually more aggressive cancers, stage for stage those women were more likely to relapse and more likely to die of their cancers. The first medication to come along that could essentially inactivate the HER2, and be used to treat HER2 positive cancer, was called Herceptin, and it's the one you just alluded to, it's an antibody against the HER2 protein, and what we found in the initial results that were available around 1995, was that for the patients diagnosed with early stage HER2 positive breast cancer, if you add Herceptin into their treatment you reduce their risk of relapsing by an additional 50% above and beyond the benefit they would have already received from conventional chemotherapy or anti-estrogen pills, and that kind of breakthrough in one new medication is as big a step as we often see in the treatment of any type of cancer.Chu

The treatment of breast cancer really has evolved over the past few years as Francine has said and in many ways I think it may represent kind of the model for this so called individualized, personalized therapy. Are there other types of targeted therapies that are now being used to treat women with breast cancer?DiGiovanna Experimentally there are. You used the word targeted, and the kind of catch phrase that we use now for some of the new types of treatments that we are having for cancers in general are what's called 'targeted therapies', meaning new types of medicine that aren't the conventional type of chemotherapy that we have used for the last 50 years and they tend to not have the kind of side effects that conventional chemotherapy can as well. And breast cancer has really led in this field as you alluded to for many years, for decades we have been treating that estrogen receptor type of breast cancer with anti-estrogens and that's really the first example of a successful non-chemotherapy treatment for any type of cancer, targeted therapy as we are calling it. And then the second most prominent example, and breast cancer led the way again, in the modern era was Herceptin for treating HER2 positive type of breast cancer. And now in a number of other types of breast cancers some of these targeted therapies have been extremely effective as well and experimentally now we are also using other targets in breast cancer to see if they are suitable either as individual therapies or in conjunction with the anti-estrogens or the Herceptin types of therapies.Foss Mike, you are doing some specific research in this area looking at signal transduction pathways in breast cancer, can you tell us a little bit about that?DiGiovanna Yes, so one of the things that I was very interested in was combining targeted therapies and so early on my lab studied in the laboratory and in mice with breast cancers the promise of combining HER2 directed therapy like Herceptin with anti-estrogens, and in the laboratory it was quite a significant and dramatic effect and it's being used in patients now, although without as dramatic results as we saw in the laboratory. In my laboratory we began to wonder why it's not as dramatic in patients as it is in the lab and that led us to explore another receptor to potentially target for24:01 into mp3 file http://yalecancercenter.org/podcast/may3110-cancer-answers-DiGiovanna.mp3 therapy called the insulin-like growth factor receptor, or the IGF-1 receptor. And the reason why we became interested in that is it turns out that this IGF-1 receptor can work in conjunction with the estrogen receptor or in conjunction with HER2, and it turns out that this IGF-1 receptor can become over-activated to cause resistance to the anti-estrogens or resistance to the HER2 directed therapies such as Herceptin. And so a number of pharmaceutical companies have been interested in this and now are developing drugs to target this IGF-1 receptor and we have been working with one such of those compounds in the laboratory and found that in breast cancer cells growing in Petri dish, or in mice with breast cancer tumors growing, that combining these IGF-1 receptor inhibitors with either anti-estrogens or Herceptin seems to give a dramatic beneficial effect as well and so actually the very earliest trials are just beginning to be conducted in women with breast cancer of these experimental types of therapies.Chu Are there any other types of new targeted therapies that look particularly promising?DiGiovanna Yes, in

another experimental area there is a class of drugs that are called the PARP inhibitors and the PARP stands for poly(ADP-ribose) phosphorylase and this is an enzyme that is very important in the repair of DNA. Many of our chemotherapy drugs kill cancer by damaging the cancerous DNA and it turns out, especially for the women who have mutations in the BRCA1 and BRCA2, that the important role of BRCA1 and BRCA2 is in repairing DNA. And there are basically two pathways that a cancer cell can use to repair its DNA, and that is either the BRCA1 and BRCA2 pathway or the other pathway that uses PARP. So if a woman has a cancer with BRCA1 or BRCA2 mutation that means that pathway is shutdown and defective. So, if we treatment them with a PARP inhibitor that can shutdown the other path that they have to repair their DNA, they are left with no way possible left to repair their DNA. Just in the past year, we have had two studies using PARP inhibitors that have shown great promise in treating woman with BRCA1 or BRCA2 mutations and in treating women with the breast cancer that we call triple negative, because those are the cancers that don't have estrogen receptors or progesterone receptors or HER2 and these triple negative tumors, although they don't have mutations in BRCA1 and BRCA2, they seem to have defects in that same pathway, so they are also highly susceptible to these PARP inhibitors. After we have had, in the past year, these very exciting results in several small trials, there are now larger trials going on and we expect this may be a rapidly developing area where this type of medication may be available in the near future.Foss Are these PARP inhibitors oral or intravenous? And are there major side effects associated with them?DiGiovanna There are several PARP inhibitors being developed by several different pharmaceutical companies and one of them is intravenous and another one is oral, so there are both types. The side effects27:27 into mp3 file http://yalecancercenter.org/podcast/may3110-cancer-answers-DiGiovanna.mp3 seem to be quite minimal and that's probably because normal cells in the rest of the body have very little PARP and don't rely on PARP very much, it's cancer cells that have high levels of PARP. So the side effects, even when added to conventional chemotherapy, don't seem to add any significant amount of additional side effects compared to conventional chemotherapy.Chu Mike, I understand that your group here at Yale Cancer Center has also been studying one of these PARP inhibitors.DiGiovanna Yes, we have a clinical trial that's going on right now combining one of these PARP inhibitors, it happens to be the intravenous one, in combination with a conventional chemotherapy drug.Chu And do you have any sense of the results thus far?DiGiovanna This is a phase 2 trial and so we don't have a large number of patients enrolled at this time and it's also a national trial, so there are just a few patients at each center, at a number of different centers across the country, but I can simply say anecdotically that patients I have had on it are having very nice responses to it at this time.Foss When you think about the treatment of breast cancer, this is a chronic disease for a lot of women, how tolerable are all these therapies over periods of time?DiGiovanna Fortunately the PARP inhibitors, as I said, have almost no side effects. When you add it to chemotherapy you can't see any additional side effects and

when it's being used as a single agent without chemotherapy, there is very little in the way of side effects. Anti-estrogens are used typically even in women with curable phases of the disease. We treat women for at least five years and we are experimenting with ten years now of anti-estrogen therapy, they can have their own peculiar side effects, but they are quite tolerable and even the HER2 directed therapies are quite tolerable especially when the chemotherapy portion is finished and the women are simply taking the Herceptin or the other types of therapies that target HER2.Chu Many women complain about the development of hot flashes when they are treated with anti-hormonal therapy, what are your suggestions, recommendations for trying to treat that side effect?DiGiovanna So for women who are treated with anti-estrogen pills of any type that is the most common side effect, hot flashes as if a women is going through menopause. The explanation being that when women get hot flashes when they go through menopause, their estrogen levels are dropping as they go from premenopausal to postmenopausal and so anti-estrogen pills can mimic that side effect, and for most women its mild, for some women its more severe and difficult, and there is no absolute therapy that can make them disappear but there are a number of different things that can30:08 into mp3 file http://yalecancercenter.org/podcast/may3110-cancer-answers-DiGiovanna.mp3 help and the thing that we use commonly that seems to help the best is a very low dose of certain types of antidepressants, lower than the dose you would even use to treat depression, but even baby doses can be quite effective at relieving those. Other things can be simply environmental maneuvers such as having a fan on ones desk or a fan above ones bed blowing some cool air on a person. And other women have experimented with other things including acupuncture or meditation to help to relieve hot flashes. They tend to subside on their own overtime even without any intervention.Chu And what about the potential role of soy, soy products, to help relieve symptoms?DiGiovanna Some women do find that soy can help and it's probably because there are weak plant estrogens in soy and so for some types of anti-estrogen therapies we feel that, that's acceptable to use soy, with other types of anti-estrogen therapies particularly the type called aromatase inhibitors, we worry a little bit that we might be giving back some estrogen in soy all be it a very weak plant type of estrogen.Chu Mike, as always it's been great having you on the show to discuss the latest in terms of the evaluation and treatment of breast cancer and we look forward to having you on a future show.DiGiovanna Thank you.Chu Until next week, this is Dr. Ed Chu from Yale Cancer Center wishing you a safe and healthy week.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.