Support comes from AstraZeneca, the Beyond Pink Campaign aims to empower metastatic breast cancer patients and their loved ones to learn more about their diagnosis and make informed decisions. Learn more information lifebeyondpink.com Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers is our way of providing you with the most up-to-date information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week it is a conversation about the overdiagnosis of breast cancer with Dr. Donald Lannin. Dr. Lannin is a Professor of Surgery at Yale School of Medicine, and Dr. Chagpar is an Associate Professor in the Department of Surgery at Yale School of Medicine and the Assistant Director for Global Oncology at Yale Comprehensive Cancer Center. Chagpar Don, you know we have heard a lot in the media and the press about this concept of overdiagnosis, and for a lot of the women who are listening right now, they may be thinking what do you mean overdiagnosis? I go for my mammogram and the reason I go is to try to find cancer early. So, help us to understand this whole concept. Lannin Well, what we are finding out is that a lot of early cancers are not really serious. There are cancers that when we talk about overdiagnosis, we do not mean that somebody made a mistake and diagnosed something as cancer that was not cancer. It is a cancer, but it is a very slow growing indolent cancer that would probably never cause the patient any problem the rest of her life if it were not found. Now, we have known for at least the last 5 or 6 years that there is a degree of overdiagnosis, but we have not really known which patients could be overdiagnosed or how they are overdiagnosed or how that whole thing works. It is sort of muddy, and the way we knew that it exists is if we look at cancers over the last 30 years since mammography screening became very widespread, the number of cancers went up tremendously, but mostly the number of small cancers went up, and if you look at the number of large cancers that are life threatening and cause a problem, they went down a little but they did not go down very much. So, small cancers actually increased in incidence in over three times as much as large cancers decreased. So, that kind of let us know that there was some overdiagnosis going on. Chagpar But, is it not that what screening was supposed to do, is it not that screening was supposed to find more small cancers before it got to be big cancer so that you could pick up your cancer really early when it was the most treatable? 00:02:54 into MP3: https://ysm-websites-live-prod.azureedge.net/cancer/2018-yca-0128-podcast-lannin_326163_5_v1.mp3 Lannin Well, you are exactly right. That was the whole philosphophy or the rationale behind screening, but what we found is that they are not picking up the same cancers and it is kind of interesting, we have small cancers, say under 2 cm; we have medium-sized cancers, maybe 2-5 cm; and then the large cancers, over 5 cm. And we always thought that what we have known for over a hundred years that the size of the cancer correlates with the survival. So, the small cancers have very good survival, the large cancers have poor survival and the medium ones are kind of in between. So, until recently though, over the last hundred years, for 90 of those years, we thought that breast cancer was one disease that the small cancers turned into

the medium cancers and the medium cancers turned into the large cancers, and if that were true, it would make sense that finding the cancers when they are small would prevent the cancers from becoming a problem when they get large, but what we are finding now is the whole concept is wrong; the small cancers, most of them will not become large and the ones that are large, do not come from the average small cancer and they come from a very rare subset of small cancers. So, the premise is false that the reason large cancers are bad and small cancers are good they're not because we caught it earlier, but because the large cancers are biologically different and they are much more dangerous, where the small cancers are very slow growing and not dangerous. Chagpar So, it comes down to tumor biology. So, tell us more about the different kind of biologic subtypes and which kinds you tend to pick up on mammography that are overdiagnosed versus which types you really want to pick up on mammography because those are worse biologically. Lannin So, biology is really the holy grail of what we would like to really understand, and there are all different types of molecular studies that are coming along for breast cancer. It is very common now they use something like the Oncotype or the MammaPrint that are molecular studies. And then are a lot of ones that are not even that commercialized yet that are being studied. But part of the problem is even the Oncotype and the MammaPrint, you do not have large data sets that have those results in them. So, in an article we did recently, we looked at something even simpler, just the tumor grade and the receptor status – whether it had estrogen or progesterone receptors. And we found that just with those three very primitive biological tests, we could categorize tumors as favorable, intermediate or unfavorable. So, what we found is that the favorable ones are the low grade, grade 1 hormone receptor positive, so ER or PR positive cancers, and those are pretty favorable. The 10-year breast cancer specific survival is about 97 or 98% for those cancers, but then if you look at the unfavorable ones, they are the grade 2 or 3 receptor negative ones or the grade 3 ones that did not have both the ER and PR, had one or the other, those ones were pretty unfavorable and had much worse survival. And then if you looked at the incidence though, the cancers that are now very common that are picked up very small on the mammogram are the favorable ones. They are the low-grade hormone receptor positive ones; where the unfavorable ones are not picked up in the mammogram because they grow so quickly that they become large before you could find them on the mammogram. Once in a while, there is an exception. I saw a patient recently that had a cancer diagnosed because it became palpable I think in August and she had a mammogram 5 months earlier in March that was read as normal, and so we were interested. 00:07:14 into MP3: https://ysm-websites-live-prod.azureedge.net/cancer/2018-yca-0128-podcast-lannin_326163_5_v1.mp3 Lannin cont.d We looked back at that mammogram, and in retrospect on one view, we could see a small less than 1 cm nodule. But then in 5 months, that had grown into 3-cm large cancer. And the reason that it does not happen very often is because it was just a coincidence, we had the mammogram in March and could see it then. If we had gotten the mammogram in January, it would not have shown up at all because it would not have been there. If we had gotten in April or May, it would have already been

much bigger and well on the way to the 3-cm mass. So, to find a cancer that is fast growing like that, you have to hit the mammogram just right to the month, to see when it is small. So, most of the small cancers we see on the mammogram, if you look back a year or two before, you can usually see them then too. So, they grow just very slowly over many years and the lead time is actually an important variable, and what the lead time is, is the time from when you can detect it on the mammogram to when it would become obvious clinically or be a palpable mass that could be found without the mammogram, and back in the 1960s when mammography was being proposed as a good solution to the breast cancer problem, we felt that the lead time for most tumors was 3-4 years and we knew that some tumors grew a little more quickly and some a little less quickly, but we thought well maybe a faster growing one, the lead time would be 1 or 2 years and a slow growing one, it might be 5 or 6 years, but what we have found recently is the lead time varies much more radically. There is a large group of fast-growing cancers where the lead time is less than a year and these are typically ones that are called interval cancers, and then there is a very large group of very slow-growing cancers where the lead time is 10-20 years, and these are the ones that are being picked up very frequently on mammography because they are slowly growing that if you do not find it one year, you will see it the next year or the next year and eventually it is going to be detected, but many of those grow so slowly that the lead time is 10 or 20 years before it would ever become big enough to feel, and of course, it depends on the age of the woman, but many women may not live 10 or 20 years, so for older women especially, the cancers that we find on the mammogram many of them are totally irrelevant and they are not going to cause the patient a problem. Chagpar So, that brings up an interesting question and certainly one that has come up in the media and we have talked about it on this show in the past as well, which is these screening guidelines, they tend to be changed periodically and most recently people have started questioning when women should stop having mammograms. So, to your point which is with regards to lead time and being older, is there a particular age at which the patients should really just stop having mammograms? Lannin Well, I am not individually come up with guidelines. I think the guidelines need to be assessed by committees and groups and so forth and come to some consensus, but I am not proposing that we stop doing mammograms, but I think it would make a lot of sense to stop doing maybe by age 70 or so. If we look at the overdiagnosis, it is very age dependent and the older women are much more likely to be overdiagnosed than younger women, and the benefit of early detection is much less in older women. So, by the time a woman is in her 70s, the chances are much greater that even if the mammogram shows a cancer, it is probably a cancer that would not bother her. So, my own personal thought is maybe groups that promulgate these guidelines should consider maybe stopping by age 70 instead like very frequently now we go into the 80s or late 80s even. 00:11:45 into MP3: https://ysm-websites-live-prod.azureedge.net/cancer/2018-yca-0128-podcast-lannin_326163_5_v1.mp3 Chagpar Yes. So, I think a number of guidelines now have suggested that you stop, and all of the guidelines, are a little bit different, some say by the age of 70, some say by the age of 75 and some

say to use your magic crystal ball and stop having mammograms when you are within 10 years of passing away, not that my crystal ball tends to work that well, but maybe that is why, but with regard to the interval cancer, some may argue that is a reason to do mammograms even more frequently because especially for the fast-growing cancers, you want to pick them up and as you say, if it is really about making sure that the mammogram gets time just right and you do not know when just right is, should there be some women who get mammograms more frequently than once a year? Lannin Well, that has definitely been considered. The problem with that is all the mammograms have false positive results. So, out of 100 mammograms, something like 5 or 10 are going to be called back for additional views and probably a couple percent are going to need biopsies and so the more often you do it, the more often you have these false positives and these unnecessary biopsies. And of course, the expense goes up tremendously. So, I think it is hard to reach a happy medium, but in general the trend has been to do them less often. A few years ago, most of the groups recommended doing them yearly, and now actually most of the groups recommend doing it every other year. Chagpar Alright, well that certainly has caused quite a lot of controversy in the public, but we are going to take a short break for a medical minute and then we are going to come back and talk more about overdiagnosis with my guest Dr. Donald Lannin. Medical Minute Support comes from AstraZeneca, working to change how cancer is treated with personalized medicine. Learn more at astrazeneca-us.com. It is estimated that over 200,000 men in the US will be diagnosed with prostate cancer this year with almost 3000 new cases in Connecticut alone. One in six American men will develop prostate cancer in the course of his life time. 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 2 simple tests, a physical exam and a blood test. Clinical trials are currently underway to test innovative new treatments for prostate cancer. The Artemis machine is a new technology being used at Smilow Cancer Hospital that enables targeted biopsies to be performed as opposed to unnecessarily removing multiple cores from the prostate. More information is available at YaleCancerCenter.org. You are listening to WNPR, Connecticut's public media source for news and ideas. 00:15:01 into MP3: https://ysm-websites-live-prod.azureedge.net/cancer/2018-yca-0128-podcast-lannin_326163_5_v1.mp3 Chagpar Welcome back. This is Dr. Anees Chagpar and my guest Dr. Don Lannin. He is here with me tonight to talk about overdiagnosis for breast cancer and this whole concept of overdiagnosis is really the idea that some cancers that are picked up on mammograms are so indolent, so slow growing that they really would not cause you any trouble anyways and that likely they would cause you no harm. On the other hand, there are some cancers that are rapidly growing where they show up in the interval between mammograms, and so Dr. Lannin, one of the questions that people may have is, is there a strategy whereby if you know a cancer is slow growing, you can simply watch it instead of having it treated or are these cancers such that they have the potential to cause both physiologic and psychologic harm

such that women may just want to have them removed regardless. Lannin Well, I think both are true, certainly for prostate cancer, watchful waiting is becoming much more common and very well accepted. The difference is surgery for prostate cancer has a lot of side effects and it is not a very popular surgery where the surgery for breast cancer, at least if you can do just a simple lumpectomy, it is actually very easy. A lumpectomy is just an outpatient procedure and is not generally deforming or have many side effects. So, I do not think that there is many women that would feel real strongly about avoiding a lumpectomy if that is an option. Now, avoiding some of the other treatments like mastectomy or axillary node surgery or the postoperative treatments like radiation therapy or chemotherapy, certainly there is a big advantage in avoiding those. So, my own feeling is that the cancers that we call overdiagnosed, unless the person is very elderly like in the 90s or has a lot of comorbidities where even a lumpectomy is kind of a big deal, those patients would be ideal and even now we do watch many of those. But for a healthier patient, I think most patients are going to feel better having a lumpectomy and knowing it is out, but then hopefully we can then avoid the radiation or the axillary surgery or the other things that frequently go along with it. Chagpar So, when you talk about overdiagnosis, just to be clear you are not advocating that people do less mammograms simply because mammograms may find these cancers and that they then may mandate surgery, but what you are really talking about is over-treatment and having additional therapies for a cancer that may be indolent? Lannin That's right. I think they go hand in hand, and as I mentioned, I am not advocating we do not mammograms, and I think stopping mammograms by age 70 might somewhat decrease the rate of overdiagnosis in the elderly women, but probably a better approach is to understand the biology of the cancer and if we find a cancer, diagnose it and then try to understand which ones we do not have to treat so aggressively. Chagpar Which brings us to this paper that you wrote in the New England Journal. Tell us more about that. 00:18:47 into MP3: https://ysm-websites-live-prod.azureedge.net/cancer/2018-yca-0128-podcast-lannin_326163_5_v1.mp3 Lannin Well, that was a very fun paper. It was really initially a response to a previous paper written by Dr. Gilbert Welsh and he is the one that showed that the small breast cancers were increasing so much and the large breast cancers only going down a little bit, and so my collaborator, Dr. Che Wang, we were trying to look to see if we could find data to support that paper that Dr. Welsh wrote and also to understand the mechanism how that would happen, and so that is how we came up with a classification of using the grade and estrogen and progesterone receptor to divide patients in the favorable, intermediate and unfavorable groups. And then, Dr. Wang did some very elegant models where he looked at the lifespan expectancy of patients and the chance that the cancer would be overdiagnosed, and then from that could calculate the lead time. It turns out if you know the life expectancy and either the lead time or the rate of overdiagnosis, you can calculate the third one. And so, he built some very elegant models looking at who is overdiagnosed and how that happens, and as I mentioned, we had known that there was some degree of overdiagnosis but we did not know really who it was or what tumors, and

now we can see pretty clearly that it gets more and more common, the older the patient is and it is much more common with the favorable tumors than the unfavorable tumors. So, for the first time we can kind of narrow in on who is being overdiagnosed. Chagpar So, to be clear when we say that they are being overdiagnosed, how exactly was that defined in the paper? Lannin Well, what we did is take Dr. Welsh's finding that there was 22%, so 22% of all the breast cancers that we have seen nowadays we think are overdiagnosed, but that 22%, that is a little nebulous, you do not know still which ones, and what we have found is we could come up with that 22% figure by making it higher in older patients and higher in ones with favorable tumors and then much lower in younger patients and patients with unfavorable tumors. Chagpar So, this idea, because we know that in general if you just look at the general population, most people who get breast cancer get favorable tumors, I mean they get ER/PR positive cancers that are far more common than triple-negative cancers. Lannin Right. But the grade is a very important difference. The grade 3 ER positive but PR negative cancers actually have a pretty poor prognosis, so it is not just a question of the hormone receptors, it is really the grade 1 cancers are the real slow growing ones, unless they happen to not have either any of the receptors, then they can be bad even at grade 1, but that correlates better with the growth rate and the overdiagnosis than just the hormone receptors. Chagpar So, it seems to me that what we are really talking about is overtreatment, because if we still get mammograms in everybody, in order to really understand who has a favorable tumor and who does not, those patients would still need to have a biopsy and therefore be diagnosed. So, how do we really get around the problem of overdiagnosis or is the term just a misnomer. 00:22:52 into MP3: https://ysm-websites-live-prod.azureedge.net/cancer/2018-yca-0128-podcast-lannin_326163_5_v1.mp3 Lannin Well, as I mentioned, overdiagnosis does not mean anybody did anything wrong, it just means that the cancers that would not have bothered the patient if they had not been diagnosed, and you are right, I think the ultimate key is going to be to better understand the biology and I want to make clear that with our current technology, we cannot on an individual level, say "Mrs. Smith, your cancer is overdiagnosed." That is what we would like to be able to do, but we cannot do that. What we can do is say if we had a 100 patients like Mrs. Smith, two-thirds of them would be overdiagnosed, but we cannot ever say that an individual patient is overdiagnosed, so at this point, we are really not to the point where we can say we do not want to treat somebody, but we can say we can individualize their treatments, and I think there is already situations particularly in women over 70 where we know we can treat less aggressively with radiation, there is some guidelines that we may not need to do sentinel node biopsies in women over 70 and yet both radiation and sentinel node biopsy may have a role in some women over 70, but so by categorizing the patients in the favorable and unfavorable biology, it may help us decide how to treat women over 70 without going necessarily against guidelines and recommending no treatment at all. Chagpar What about the use of additional techniques. So, here in Connecticut, there was a dense breast law passed and this law has now been passed in many states all over the nation,

which really helps women to understand who has dense breasts and who does not, and in the women who have dense breasts, the idea is that you may need additional screening to really look carefully in the breast and see if we can find cancers. With your research looking at overdiagnosis, does that fly in the face of this whole dense breasts and trying to find things that you cannot even see on mammography. Lannin Well, probably, we really do not know. I think the question of ultrasound screening for dense breast is a fascinating one because it was based on no science whatsoever. The only thing we know about screening ultrasound is that occasionally you will find cancers that do not show up on a mammogram, but that is the only thing we know. We do not know, some of our data actually suggests that ultrasound-detected cancers are more likely to be overdiagnosed than even mammogram detected cancers, but we need much better figures on that. But the big question that we do not know, is would the survival be just as good if we did not do the ultrasound and waited another year or two and then found that cancer on a mammogram. Well the odds are very good that the survival would be just as good, but that is the real question that needs to be asked and nobody is asking it. But so, the way this law got passed is absolutely fascinating with no data whatsoever to suggest that it is worthwhile. The legislators based on one or two patient situations or case stories assumed that early detection is always better and so they passed a law encouraging screening ultrasound, and now it is being passed half of the states in the country without data. So, it is, I think, interesting when in some ways we try to be rigorous about applying science to technology into public policy and health policy and yet something like screening ultrasounds get passed based really on a myth and the myth is really that early diagnosis is always better. 00:27:07 into MP3: https://ysm-websites-live-prod.azureedge.net/cancer/2018-yca-0128-podcast-lannin_326163_5_v1.mp3 Chagpar I mean it goes to other forms of imaging as well, I mean in the past, almost every patient who had a mammogram and was diagnosed with even a small cancer would have an MRI – the idea behind that being that the MRI might show more cancers, but if those cancers did not even show up on the mammogram, were those overdiagnosed too? Lannin They may be. Some of the data we have suggested MRI-detected cancers are also maybe a little more likely to be overdiagnosed than mammographically detected cancers. But I think there are places where an MRI is helpful, but we are actually much less likely now to just apply it routinely to every newly diagnosed breast cancer and we are much more selective where we use it. Chagpar Right, and in fact, now there are national guidelines that suggest that you do not routinely use it in every newly diagnosed breast cancer patient, and to your point, really start to be a little bit more selective and individualized in terms of whom you order an MRI. So, after the publication of your study, which talked about overdiagnosis and kind of thinking about less favorable versus more favorable cancers and how the favorable cancers tend to be overdiagnosed, particularly in elderly patients, have you noticed any change in practice? Lannin Well, our study was not really to the point where we made any recommendations about changing the practice, it was more to understand really the mechanism of overdiagnosis and understand what is going on. Now, I think the next steps are

going to need some clinical trials and much better measures of tumor biology to really carry that to the next level to say the patient with a favorable cancer by XY and Z criteria, you can do less treatment and certainly those trials are being designed and I am quite hopeful that we will get some progress there. Dr. Donald Lannin is a Professor of Surgery at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu, and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer. You are on WNPR, Connecticut's public media source for news and ideas.