WNPR Radio Voice [00:00:00 – 00:00:26] "Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital. Welcome to Yale Cancer Answers with the director of the Yale Cancer Center, Dr. Eric Winer. Yale Cancer Answers features conversations with oncologists and specialists who are on the forefront of the battle to fight cancer. Here's Dr. Winer." Dr. Eric Winer [00:00:26 – 00:01:08] "We're going to talk about the global fight against cancer and where we stand. As you know, cancer is, of course, a common problem in the United States. It is even more devastating globally. And as the rates of cancer—the incidence of cancer—rises in many countries around the world, unfortunately, treatments are not always available in many of those countries. So to help us better understand where we stand with this global fight with cancer, we have Dr. Daniel O'Neil, who is an expert in global health. Dan is an assistant professor of medicine in medical oncology at the Yale School of Medicine and Yale Cancer Center. He is a breast cancer doctor, a breast cancer medical oncologist, and sees patients largely in Waterbury, Connecticut. His research has focused over the last several years on breast cancer in sub-Saharan Africa, and in particular, research focused on how we can improve the early diagnosis of breast cancer in countries in that region. So, Dan, it's really a pleasure to have you here this evening." Dr. Dan O'Neil [00:01:09 – 00:01:48] "Hi, Eric. Thank you. Yes, it's great to be here, and I'm looking forward to talking about this important and large topic." Dr. Eric Winer "It is big, and I think it's fair, generally speaking, to talk about breast cancer, and people can extrapolate to all cancers. When, in fact, you want to talk about all cancers, that's fine. But you are a breast cancer expert, and everything we see in breast cancer is really true in terms of other cancers as well. So people can just do a little multiplication. So first, how big is the breast cancer problem globally?" Dr. Dan O'Neil [00:01:49 – 00:03:38] "Well, it's, I think, bigger than a lot of people realize. I think when we're used to thinking about global health—or global health in the popular imagination—people often think about infectious illness. And infectious disease is still a big problem. You know, sometimes people talk about a double burden of disease, meaning that in low- and middle-income countries—the sort of countries that we're talking about—while you still have issues with infectious disease, be it HIV, tuberculosis, or other examples, there really is, as these countries have been developing, as life expectancy has been increasing, as risk factors that were pioneered or that we learned about in high-income settings, as those risk factors reach LMICs, non-communicable diseases, including cancer, are on the rise as well. So thinking about breast cancer specifically, in almost every country in the world, breast cancer is the first or the second most common cancer in women. And in places where it's the second, cervical cancer is the first. But in most countries, breast cancer is the most common cancer among women. And what's also, I think, important to understand is that breast cancer in a low- or middle-income country tends to be a lot more deadly than a breast cancer diagnosed in a high-income setting—in, you know, the United States, Canada, and Europe. You can compare incidence rates and you can compare mortality rates. Incidence rates describe how frequently the cancer is diagnosed, and mortality rates describe how frequently a person of a given age is going

to die of a specific cancer. Incidence rates for breast cancer in high-income countries are much higher than in low-income countries, and the likelihood of being diagnosed with breast cancer is still higher if you're living in America, if you're living in Europe. But for a person of a given age, you're actually slightly more likely to die of breast cancer in some middle-income countries. And the likelihood of dying of breast cancer if you are diagnosed with it in almost all low- and middle-income countries is two to three times as high as the likelihood of dying of breast cancer following diagnosis in high-income settings." Dr. Eric Winer [00:03:38 – 00:05:08] "And that's really because of two reasons, at least. One, of course, is that early detection is not common—in some cases, nonexistent—in many of these countries. And the other, of course, is that treatment just isn't available in the same way." Dr. Dan O'Neil "Yeah, that's absolutely the case. And both fronts, you know, a useful framework, I think, for thinking about the gaps in breast cancer care comes from the W.H.O. and their Breast Global Health Initiative. So this is a program that they started in 2021. The W.H.O.'s role is frequently to issue guidelines, issue kind of development goals, health development goals. And what the Breast Health Global Initiative does is for breast cancer, it describes three real areas of need with improving breast cancer care. Two of those are exactly what you alluded to. The first is earlier detection, or in some places, screening. The second is rapid diagnosis, because that's actually a big gap too. The period of time it takes between the first time somebody walks into their doctor's office and says, 'Hey, I think something's going on with my breast,' to the point where you can actually pathologically confirm that they have breast cancer—that can take months, and that's time that the disease is growing, too. And then the third is completing treatment—completing multidisciplinary treatment." Dr. Eric Winer [00:05:08 – 00:07:02] "Yeah, I mean, I have to say, the delay in establishing a diagnosis is not something that would have occurred to me. You know, in the United States, typically someone goes to see their doctor, has a lump, or in some cases, of course, has an abnormal mammogram, and gets the diagnosis. The delay—there isn't much of a delay for most people. I mean, usually a diagnosis is made certainly within a month. And it sounds like in many other parts of the world, it could be months and months." Dr. Dan O'Neil "Yes, yeah, I mean, absolutely, there is certainly a potential for that. And these problems are so complex. There's a potential for failure at really multiple—so many levels." Dr. Eric Winer "So many levels." Dr. Dan O'Neil "Yes, exactly. You know, if you're thinking about time to diagnosis, you're already taking for granted the fact that a woman has noticed a problem in her breast, has identified that as a problem, realizes that she needs to have it evaluated, and has gone to a doctor's office. That's not simple. You can't always assume that is going to happen. But take it for granted that does happen. When she gets to the doctor's office, you need the physician who sees her—who's most likely a primary care specialist—to recognize the potential for breast cancer. There are very well-trained, very competent primary care doctors operating in a lot of these places, but cancer's not always at the front of their mind. So that awareness is not always there to prompt people to act rapidly. And there are studies showing that many women, on the road

to diagnosis, see several providers before they're even referred for imaging and diagnosis. They might be treated for a breast infection or something along those lines. So you have to have the recognition at the provider level. And then you enter the stream of needing imaging, a biopsy, a pathologist to read your biopsy. And there are usually shortages in terms of supply for all of those things, and so there can be waits that add up." Dr. Eric Winer [00:07:02 – 00:09:21] "And of course, you know, in the United States several decades ago, breast cancer was a diagnosis that oftentimes people understood poorly, that women would often hide the diagnosis because of shame and a whole range of different emotions. And I think much of that in the United States has really gone by the wayside. But that's not the case in many other countries. And cancer is poorly understood. There are places where it's still thought to be contagious and where there is still shame and a great deal of hesitancy about coming forward with the diagnosis." Dr. Dan O'Neil "Yeah, absolutely. So there can be quite a bit of stigma associated with a cancer diagnosis, period. You can layer on top of that, when you're thinking about breast cancer, stigma related to potential treatments that include removal of the breast, which is still more common outside of the U.S. and outside of Western Europe than it is here, where so much more frequently we are able to do more conservative surgeries and avoid mastectomies when, you know, when women want to take that approach. Whereas in many other places, that's so much less common, and there's a lot of reasons for that. These things have cascading effects. You know, you're usually seeing women with larger tumors, which make breast-conserving surgery more difficult. And you might have access to surgery and chemotherapy, but not radiation. And if you don't have access to radiation, you know, for folks who are listening, this isn't true 100% of the time, but most of the time, if you have a lumpectomy or breast-conserving surgery, in order to make that as an effective strategy as a mastectomy, radiation follows your surgery." Dr. Eric Winer [00:09:21 – 00:11:05] "And what are the areas in the world where you think that we face the biggest challenges—or people there face the biggest challenges? Obviously, the United States, Western Europe, Australia—these are all places where care is really quite sophisticated. Increasingly, care is at a very similar level in parts of Asia. So Japan has had advanced care for a long time. China has really come a tremendously far way in the last decade even. But that's not true everywhere. And what are some of the places that make you most concerned?" Dr. Dan O'Neil "I—you know, there is a range of experience, just like there's a sort of range of income levels. When we say low- and middle-income countries, that can describe a lot of different scenarios. And because ultimately, the constraints in cancer care do come down to available resources to devote to a public health system, to devote to cancer care. You know, how much or how little there is often depends on—it often looks similar to the overall development picture, I guess. So in the poorest countries in sub-Saharan Africa, as you might imagine, they have the least in the way of cancer care. Sub-Saharan Africa has low-, middle-, and upper-middle-income countries, where areas are more sophisticated. There are parts of Asia, like Southeast Asia, where care is somewhat more sophisticated, but there's plenty of room for improvement. And

so it's a range." Dr. Eric Winer [00:11:05 – 00:13:27] "Yeah, no, it, of course, is just a huge challenge. So when we come back, which we're going to do in just a minute or so, we're going to talk about drug prices and the challenge that we face with that. And then I'd like to move on and talk a little bit about both your own research related to earlier detection of breast cancer and some new technologies that may be helpful in moving all cancer care forward in and around the world. So we will be back in just a minute. Dan, I want to thank you for being with us so far. But there's more to come."

WNPR Radio Voice [00:13:27 – 00:13:53] "Funding for Yale Cancer Answers comes from Smilow Cancer Hospital, where a team of specialists provide genetic testing to inform patients of their cancer risk. Learn more about Smilow's Genetics and Prevention Program at SmilowCancerHospital.org." WNPR Radio Voice [00:13:53 – 00:14:27] "There are over 16.9 million cancer survivors in the U.S. and over 240,000 here in Connecticut. Completing treatment for cancer is a very exciting milestone, but cancer and its treatment can be a life-changing experience. The return to normal activities and relationships may be difficult, and cancer survivors may face other long-term side effects of cancer, including heart problems, osteoporosis, fertility issues, and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers, such as the Yale Cancer Center and Smilow Cancer Hospital, to keep cancer survivors well and focused on healthy living. The Smilow Cancer Hospital Survivorship Clinic focuses on providing guidance and direction to empower survivors to take steps to maximize their health, quality of life, and longevity. More information is available at YaleCancerCenter.org. You're listening to Connecticut Public Radio."

Dr. Eric Winer [00:14:27 – 00:16:18] "Hello again, this is Eric Winer with Yale Cancer Answers, and I'm joined tonight by our guest, Dr. Daniel O'Neil, a member of the faculty at Yale School of Medicine and the Yale Cancer Center, who is himself a breast cancer expert but is here with us tonight talking about his area of research, which relates to global health and specifically cancer around the world. I want to talk for a minute about drug prices. I think, as most people know, the price of anti-cancer drugs has skyrocketed in the past 20 years. Back 20 years ago, there were chemotherapy drugs and hormonal therapy drugs that were expensive in the way we defined them back then, which would have been 1,000or1,000or2,000 a dose. We are now talking about some of the newest drugs that can cost 20,000or20,000or30,000 a month for some oral medications, or 30,000or30,000or40,000 or $50,000 for every cycle of treatment that's given, which is often every three to four to six weeks. So it's not uncommon for a patient in the United States to rack up bills—most of which are covered by insurance—of hundreds of thousands of dollars. That doesn't work in the same way around the world. In Western Europe, drugs get approved, and then it's up to health authorities to decide what is going to be reimbursed and what isn't. But in countries in Africa, it would really be left to individuals' own resources, which makes it almost impossible to think about receiving these drugs. Is that right?" Dr. Dan O'Neil [00:16:18 – 00:18:42] "Yeah, no, that's right. In most

poor countries in the world, there is really little to no public insurance for cancer care—sometimes for primary services, but insurance for cancer care is rare. And then in the private market, most people are not paying for private health care insurance. And so patients are really responsible for paying for these medications out of their own pocket. And like you said, there are very few patients anywhere in the world who can afford to actually pay the lowest price for a lot of these drugs. And so, inevitably, you see access decrease. You quoted some of the most recent list prices for some of the absolute newest drugs, and those do kind of make your eyes pop. But it's not even just the absolute newest drugs that are out of reach. Trastuzumab is an example. So trastuzumab is used to treat HER2-positive breast cancer. It's extremely effective at doing that. It really has—I think it's fair to say—completely changed the trajectory of what it means to have HER2-positive breast cancer in high-income settings. This is a drug that was first approved by the FDA in the United States in 1998. And, Eric, you probably know better than I do, so correct me if I'm wrong." Dr. Eric Winer "No, you're absolutely right. I was around then." Dr. Dan O'Neil "Yes, it was either 1998 or 1999. And it started to be used for people with much earlier-stage breast cancer to prevent recurrences in 2005—a long time ago, 20 years ago. South Africa is probably sub-Saharan Africa's most advanced economy. It is definitely the absolute largest economy in sub-Saharan Africa. It is a country with a fairly robust public health care system, particularly compared to its neighbors in the region. It just added trastuzumab to its public formulary and started giving it to patients adjuvantly, I think, in 2020 or 2021—over 20 years after it first became available in the United States. And this is a drug that, to be precise, one of the reasons they are able to do this now is because they're not giving trastuzumab itself; they're giving a biosimilar to trastuzumab—a drug that is biologically and practically identical but is manufactured by a different company. Even in these circumstances, use is restricted in some ways. So it's used adjuvantly for potentially curable patients, but it's still not being routinely offered to women with metastatic disease. And this is a drug that saves lives. So what we're talking about is lives not being saved in these countries." Dr. Eric Winer [00:18:42 – 00:19:29] "And, you know, as I've often said, the more we advance cancer therapy—and the more expensive and the more complicated it becomes—the greater the potential for disparities. Both because of financial issues and because care becomes more complicated, and you need more people to provide that kind of care." Dr. Dan O'Neil "Yeah, I don't want to be completely doom and gloom. I mean, there are efforts to try to address the price of novel cancer drugs and newer cancer drugs. For these countries, the experience with HIV and the antiretroviral therapies (ARTs) actually provides a pretty good roadmap for how to do that. When the medication came out, it was very expensive, and there were a number of different international organizations and advocacy organizations that used a variety of strategies to bring those prices down and make those drugs more accessible." Dr. Dan O'Neil [00:19:29 – 00:22:01] "There was, for example, more liberal use of generics and manufacturing of drugs with some flexibility around patent protections in certain countries. Countries pooled resources to purchase drugs together and secured discounts.

And then there were large global financing efforts. For example, the Global Fund for AIDS, Tuberculosis, and Malaria. All of these things contributed to making ARTs much more accessible. There are some of these efforts happening for cancer drugs lately. For instance, the Clinton Health Initiative has been working with the American Cancer Society on a program called the Cancer Access Program. This program is designed to negotiate directly with pharmaceutical companies to bring down drug prices and then liaise with ministries of health to help them understand what is available and how to access it at those lower prices. But there's no global fund for cancer, unfortunately, not right now. Maybe in the future—though, I don't think it's too controversial to say that there's not a lot of appetite for that at the moment." Dr. Eric Winer [00:22:01 – 00:23:01] "No, and I also think it's fair to say that the latest cancer drugs—and we have seen just an explosion in terms of therapies for cancer, therapies that are so much more effective than they used to be—but those drugs are so pricey that, unlike some of the HIV drugs, which were expensive but ultimately not drugs that would break everyone's bank, these drugs are just hugely expensive. So it is a problem. Listen, let's move on and talk a little bit about the research you are engaged in. Since that said, research focused on high-priced drugs, it's actually research focused on low-cost efforts to diagnose breast cancers a little earlier. So maybe you can tell us a little bit about what you're doing." Dr. Dan O'Neil [00:23:01 – 00:24:52] "Yeah, I'd love to. My research is focused on some of the lowest-cost, lowest-technology things that you could offer a patient. To put it in context, we've talked about some of the many reasons why there are disparities in cancer mortality and breast cancer mortality in low- and middle-income countries. One piece of the puzzle is that breast cancer tends to be diagnosed much, much later than it is in the United States. Something like—depending on the country—between 50% to 80% of women diagnosed with breast cancer in these low- and middle-income countries have stage 3 or stage 4 breast cancer at the time of their diagnosis. Stage 3 breast cancers are much harder to cure than earlier-stage breast cancers. They require a lot more invasive treatments, more intensive therapies, and more complex therapies. And stage 4 breast cancer is classically thought of as almost always incurable." Dr. Eric Winer "And in fact, even just jumping in—here in the United States, about 5% of all breast cancer diagnoses occur at a point when a woman has stage 4 disease, and probably no more than about 10% are stage 3. So you're comparing 15% versus 50% to 80%, right?" Dr. Dan O'Neil "Right, right. And one of the reasons why we see that big difference in the distribution of stages—the proportion of women who are diagnosed with late-stage disease—across these different areas is the presence of screening programs. In the United States, Europe, and in other high-income settings, we have breast cancer screening programs. Those are typically mammography programs. There are all sorts of differences in terms of which countries start mammography at which age and how frequently they do it, but essentially, there are population-level mammography programs designed to find breast cancers when they're very early, before women have noticed any symptoms. This does not exist for many low- and middle-income countries. If you want to think about sub-Saharan Africa, it essentially doesn't exist there.

Mammography is complex. It requires specialized imaging equipment. It requires radiologists to interpret all of these studies. And something that's not always appreciated is that in order to truly nudge mortality down through cancer screening programs, you really need to have extremely wide coverage. You need to screen hundreds and sometimes thousands of people to detect individual cases and save individual lives. This is just outside the scope of what many poorer countries are capable of with their public health infrastructure." Dr. Eric Winer [00:24:52 – 00:26:18] "So what are you doing to address this? What's your alternative approach to early detection?" Dr. Dan O'Neil "The work that I do looks at alternative approaches to breast cancer early detection and screening. There have been some studies—there's mixed evidence—but there are studies that show that what we call clinical breast exam can be effective. Clinical breast exam is when a trained provider—this could be a physician, a nurse, or even a lay health worker—carefully examines a woman's breasts for any sort of abnormalities: masses, but also other changes. If an abnormality is found, the woman is sent for further diagnostic imaging. Clinical breast exam has been shown, in a particularly large trial in India, to be able to downstage women—meaning to shift the proportion diagnosed with late-stage disease to earlier stages. And in older women, it has even been shown to decrease mortality as well." Dr. Dan O'Neil [00:26:18 – 00:28:09] "So the work that I do most directly is with partners in South Africa and partners in Nigeria, looking at strategies for bringing clinical breast exam as a screening tool to primary care settings. And we really focus on the implementation aspect of that. How do you structure workflows? How do you structure training? How do you select the people who do it? And how do you optimize all of those pieces to ensure that all the women you want to have screened actually get access to screening? And then, when they are screened, how do you ensure that the appropriate follow-up happens? Because, as we talked about, there can be so many points of failure in the process that we need to make sure we're not just identifying abnormalities but also connecting women to diagnosis and treatment in a timely way. It's an exciting area of work because, as we've said, these interventions are very low-cost compared to population-based mammography programs. And while they are not a replacement for mammography in a perfect world, they may be a feasible and impactful solution in places where mammography isn't currently realistic." WNPR [00:28:09 – 00:28:37] Dr. Daniel O'Neil is an assistant clinical professor of medicine in medical oncology at the 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. We hope you'll join us next time to learn more about the fight against cancer. Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital."