



Ductal Carcinoma in Situ (DCIS): Understanding Your Diagnosis and Treatment Options

February 27, 2009

Powel Brown, MD, PhD

LANITA MOSS:

... I am the current president of the YSC [Young Survival Coalition, <http://www.youngsurvival.org>], and I'm also one of the co-founders. It's always a personal joy for me to be here to see how many women have come [to this event], how many women are affected by this disease, and how many women we seem to be able to help. You guys keep coming back every year, and I appreciate it and thank you from the bottom of my heart ...

... if you've never been here before, it is the most amazing weekend you will ever experience. I promise when you go home on Sunday, you will be totally exhausted, in a good way. So enjoy yourself, meet new people, learn as much as you can ... For me, [this conference has] always been a life-changing kind of weekend. So embrace it, enjoy it, and have a great time.

For your session today, you are here for the "Ductal Carcinoma in Situ: Understanding Your Diagnosis and Treatment Options." [With us today is] ... Dr. Powel Brown ... is the Dan L. Duncan professor in the department of medicine and molecular and cellular biology at the Baylor [College of Medicine] breast center [<http://www.bcm.edu/breastcenter/>]. He's a breast medical oncologist and molecular biology researcher who has been caring for women with breast cancer for over 25 years. His research focuses on targeted medications for breast cancer prevention and treatment [<http://www.bcm.edu/breastcenter/brownlab/?PMID=11290>]. Dr. Brown is connected [with] a clinical trial testing a synthetic form of vitamin A for cancer prevention in women at high risk for developing breast cancer. He also has developed a trial to study the growth and progression of ductal carcinoma in situ. Dr. Brown is interested in studying genes and proteins to identify safe and effective targeted therapies, particularly for triple-negative breast cancers. ...

So, I think with that, [please welcome] Dr. Brown.

POWEL BROWN, MD, PhD:

... we're here to talk about ductal carcinoma in situ, otherwise known as DCIS. ... This may be a challenge, because most of you ... [either have had] breast cancer or [have] family members with breast cancer. If you're interested in DCIS, it's very possible that you've had DCIS. So I'm going to talk about detecting DCIS, treating DCIS, and what one does after you've had DCIS. Hopefully that [information serves] ... most of the people in this room ...

... I am a medical oncologist and treat patients with breast cancer. I see many patients with DCIS breast cancer. ...

Let's start with just understanding the process. Breast cancer develops over time, actually over a fairly long time, anywhere from ten to 20 years to go from normal cells [as shown here on the left] all the way into cancer. ... [What's shown here] is a duct of the breast cut [across], so it looks like a hose. Cancer arises in these ducts, and it grows and starts filling the ducts [as shown here]. When it breaks through the ducts, that's invasive breast cancer.

But it doesn't just go from normal to invasive straight away. It goes through steps along the way. Those steps include ductal hyperplasia — where there are too many cells inside the duct, but they look normal — to ductal hyperplasia with atypia, also known as Atypical Ductal Hyperplasia or ADH. [With that condition], the cells begin to look abnormal to the pathologist and there are too many of them. They're not cancer, though. These cells then fill the entire duct, and plug it sometimes, with abnormal-looking cells that look just like cancer. But they haven't yet broken through the duct. That is ductal carcinoma in situ: "in situ" meaning localized, still within the duct and not broken through.

Eventually some ... but not all of those lesions break through the duct and invade into the breast tissue, into the fatty tissue, into the stroma — that's invasive breast cancer. Now, it hasn't spread out of the breast yet — [it is] ... localized [but] invasive breast cancer. ... It has the potential to spread ... to lymph nodes or other places [as] metastatic breast cancer. ... today we're going to be talking about this step: [how] ductal carcinoma in situ [becomes invasive].

... Each step along the way, as you get closer to invasive breast cancer, one is at higher risk of developing invasive breast cancer. So a normal tissue [with the] usual hyperplasia or ... too many cells, [but cells] that don't look too bad — ... we define that as a risk of 1 ... a very slight increased risk. The Atypical Ductal Hyperplasia [ADH] or the lobular counterpart of that — that's a different part of the breast. The lobule is the part that ... secretes milk. Atypical Lobular Hyperplasia [and ADH], both ... have an increased risk [of developing invasive breast cancer] — about a four to five-fold increased risk over the normal level. If one progresses to DCIS, you have a 10- to 20-fold increased risk [of developing invasive breast cancer]. The lobular equivalent is lobular carcinoma in situ [LCIS] — that has slightly less propensity to develop invasive breast cancer, about a 5- to 10-fold.

Now, these are relative risks. If we turn that risk into percentages, it's about, in the case of LCIS — 1 to 2 percent per year of developing breast cancer once you have a diagnosis of LCIS. So in 10 years you'd have about a 10 to 20 percent chance of developing invasive breast cancer. DCIS is about a 2 to 4 percent per year risk. So in 10 years you have about a 20 to 40 percent risk of getting breast cancer. Ultimately, the idea is not to evolve to this step, which is invasive breast cancer. We'll talk about how to do that.



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In addition, it's important to know [that] while invasive cancers can metastasize and threaten your life, ... the DCIS or the LCIS ... do not carry extreme risk on their own. What they do carry is a risk of converting into a dangerous lesion — invasive breast cancer.

A couple of things to know about DCIS breast cancer: Not all DCIS breast cancers progress to invasive breast cancer. About 20 to 40 percent of women who had DCIS have it treated [and] then develop an invasive breast cancer ... more than half of the DCIS [patients] don't go into invasive breast cancer.

The problem is that we can't tell which women with DCIS will and which will not progress. ... There's a lot of research going on to try to figure that out. I'll be talking about some things we do know, that some [lesions] are more likely to progress than others. But certainly it would be better to be able to definitively tell which lesions will progress to invasive breast cancer, and treat those aggressively, and which are benign and we don't really need to worry about them.

WOMAN:

What stage would you say the DCIS is?

POWEL BROWN, MD, PhD:

... in breast cancer staging, DCIS is before Stage I. ... It's CIS ... carcinoma in situ. So the stage I, II, III and IV, that really applies to invasive breast cancer only. The DCIS is a step before that. ... The D in DCIS is ductal. So it tells that those cells are coming from a duct origin. That's to be distinguished from the L in lobular cancers. That comes from a different part of the breast. So the Ductal Carcinoma In Situ is a ductal cancer. When it breaks out into the breast tissue, it is an invasive ductal cancer. It doesn't stay DCIS, per se. CIS just means localized to the duct. Once it breaks out of the duct, it's no longer CIS. It's invasive.

WOMAN:

In your progression, your ten-year progression, you had — would you go back to that slide ... where you have ... ductal hyperplasia with atypia.

POWEL BROWN, MD, PhD:

This is the usual hyperplasia that I referred to in the other slide. This is ductal hyperplasia with atypia. Its other name is atypical ductal hyperplasia, or ADH. I think I called it ADH here. That's what you usually see.

WOMAN:

So, when someone gets examined and they see that the stage before it becomes ductal carcinoma, could they [treat that condition] ... so that doesn't develop beyond that?

POWEL BROWN, MD, PhD:

Absolutely. I guess that's a whole other talk that I'd give.

WOMAN:

The reason why I ask, because when they found a lump for me, they said it was fibroadenoma, and it would never become cancerous. They said, "If it doesn't bother you, you can leave it in there." ... So I did that. I waited two years, and then I decided to take it out. Only after I took it out did they find out it was ductal carcinoma in situ. ...

POWEL BROWN, MD, PhD:

I think, personally, I would interpret that one of two ways. [It could be that] there was a fibroadenoma, and next door to it were little cells that they hadn't detected yet that was evolving into DCIS. That's one possibility, which is very common. ... Alternatively, they [could have thought it was] a fibroadenoma [that was actually] an evolving DCIS. No way to know [which scenario actually occurred].

WOMAN:

So, it should have been that one before DCIS, right?

POWEL BROWN, MD, PhD:

Well, no, actually. I haven't shown you all the benign changes that can happen in the breast. Fibroadenoma is [different than this picture] because it's a benign lesion that virtually never evolves into a cancer. One can mistake [nly diagnose] a fibroadenoma when there is really] a cancer there, or you could have a cancer right next to it. ...

Now, to answer your other question: Can you do something about these ... risks? Why are we just talking about intervening here? The answer is, of course, "yes." Now, DCIS ... is considered cancer, so we're going to be talking about treating cancer. Everything to the left of this line, actually including LCIS, is considered not cancer. And if you're treating individuals [with precancerous tissue, that treatment is considered preventive for cancer]. We do use antiestrogens to prevent cancer. I'll be glad to talk about that after I get through the DCIS [information]. ...

WOMAN:

I just wanted to clarify: LCIS is not considered cancer, but DCIS is.

POWEL BROWN, MD, PhD:

That's a very confusing thing that I have to explain to every patient that ever comes into [my] office [with concerns like these]. It's crazy — just accept that in the beginning. [Laughter]

Invasive cancer is definitely cancer. It invades. It is potentially life-threatening if it spreads. [That part is easy to understand.] DCIS is noninvasive, [and is] not life-threatening in and of itself, but is considered cancer. [If you are diagnosed with DCIS,] your doctor will tell you, "You have breast cancer." On the other hand, if you have this lesion, lobular carcinoma in situ, your doctor will tell you, "You don't have cancer." But, in fact, [LCIS] is a high-risk lesion also.

[So, the definitions of the two diagnoses are] a little bit arbitrary. The reason this was defined this way is because we know that DCIS [that occurs] in one breast, if [left] there, will evolve right there about half the time into an invasive cancer. ... So [invasive cancer that evolves in the same location clearly came from the DCIS lesion] ... whereas with lobular carcinoma in situ, if you biopsy that and leave it there — which we often do — actually, it doesn't evolve into cancer. It[s presence] just says that [a] woman might get cancer ... in either breast. So [LCIS] is not really considered a precursor or direct precursor to invasive cancer. It's considered marking your breasts as more likely to develop cancer anywhere in the breasts. That's why we don't always resect LCIS surgically but we do always resect DCIS surgically. ...

WOMAN:

You've got a smart group. [Laughter]

POWEL BROWN, MD, PhD:

I figured that would be the case. [Laughter] You guys have really studied up because you've got the problem.

[So], first of all, DCIS is very common, [with more than] 60,000 new cases [diagnosed annually. [There are] probably about 2- to 3-fold more invasive breast cancers [found than cases of DCIS], which actually says we may need to do a better job of [making sure women get] screening. Screening can pick up DCIS [before it could become invasive cancer]. ...



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It has a lot of names, and it's very confusing when you go in and you get your diagnosis and get the pathology report. It's like, "What the hell is that?" It can be called noninvasive breast cancer. It can be called pre-invasive breast cancer. It can be called intraductal carcinoma [another term for DCIS]. It can be called DCIS.

When you get your pathology report, it will say one of these things. Ductal carcinoma in situ, that's pretty clear — DCIS, we now know what that is. Noninvasive carcinoma, intraductal carcinoma, preinvasive cancer, [are all] very common [descriptors] for pathologists to [use]. All of these things mean DCIS. . . .

When you get the pathology report, [you need to know] what the most important aspects of the pathology report are, and what the oncologist looks for. First thing we want to know is the size or extent of the DCIS. It can be really small, a millimeter or less than a millimeter. Or it can be large, taking up the entire breast. That's very important in treatment-planning. So it's critical to know the size [and] the extent of the tumor. Although on your initial biopsy, which is often done stereotactically, they don't get a size [before the surgery is done]. They just do little needle biopsies. So you don't have a sense for how big or small it is until the surgeon does the excision.

[The doctor is trying to determine] the grade of the DCIS tumor. And the grade is really a subjective thing that the pathologist calls, based on what they are looking at under the microscope, the appearance of the nuclei. . . . You clearly want to know if there's any invasive carcinoma [cancer that burst through the duct to the surrounding tissue] there. It might say, "Intraductal carcinoma with a small focus of invasion." Well, that's worrisome, and that's invasive cancer. . . .

You definitely want to know the status of your margins if you had an excision of your DCIS. . . . Your oncologist and your surgeon need to know [that as well]. . . . ["The margins are positive"] means . . . when they cut out a piece of tissue, there's an edge to the tissue [and the cancer cells remain close to the edge. In examining that tissue, a physician asks]: Are the [cancerous] cells all the way up to the edge [of the tissue that was removed], or not? We hope [the cancerous cells are] not [up to the edge of the tissue; this would be called "negative margins"]. But, with DCIS in particular, DCIS grows along the ducts, and [the cancerous cells] don't grow in a straight line. So DCIS very commonly involves a [positive] margin.

If the [cancer cells are close to the edge of the tissue the surgeon removed], one needs to go back to the surgeon and have additional surgery. [The news that you need surgery is] always upsetting to everybody, but particularly to [anyone who has already gone through a cancer diagnosis, then surgery]. After having gone through [all that] . . . you want to be done. [To] . . . go back and [have a doctor tell you], "No, I'm sorry, we have to do it again." And, in [very] rare cases, you have to do it again twice. . . .

WOMAN:

I was told that the margins could be smaller for the DCIS, that basically they were comfortable with a smaller margin than if [the same margin was present in] invasive cancer. . . . What kind of a margin would you be comfortable with?

POWEL BROWN, MD, PhD:

Everybody has a slightly different practice here. In our group — and I practice down in Houston — we consider margins kind of like pregnancy — you're either positive or you're not. [Laughter] If the margins are touching the ink — they ink the edges — if the cancer cell comes up to the ink, that's positive and that's that. If the [cancer cells don't ink the edges but] they're close [to the edges], they're negative.

. . . many of the surgeons get a little antsy if the [margins are] very close. And [if the cancer cells ink the edges in a case of] invasive cancer, because the invasive cancer is life-threatening, we definitely want to [schedule another surgery and] get that out. So it's not uncommon for the surgeons to do additional resections, even if you have close margins, although the studies don't necessarily say you have to do that.

With DCIS, there's no invasive component. So everyone, the oncologist and the surgeons, are a little more comfortable with getting close margins. . . .

WOMAN:

How close is close?

POWEL BROWN, MD, PhD:

[Again], for me, it's got to be touching. Now, there are other practices that will say within a few millimeters, we're okay, as long as it's five millimeters or more.

WOMAN:

I was wondering if there was a limit in terms of going back and having more removed for the margins.

POWEL BROWN, MD, PhD:

The first limit is to get negative margins, right? So if you can get negative margins, you do. This only applies when one does a lumpectomy, as opposed to a mastectomy. . . . It's a function of how much [tissue] you've [had] taken out, what kind of cosmetic defect you're going to have, and the size of your breast. Some people can stand to take more out than others. So, it's very individual. . . .

It's important to know whether sentinel lymph node dissection was done. That wouldn't be done, typically, on an initial biopsy. But if you had a mastectomy, [the sentinel lymph node dissection] is commonly done. Even for DCIS, it may be done by your surgeon. There's a little bit of controversy over whether one should do sentinel lymph node dissections for DCIS or not. I think everybody would do sentinel lymph node dissections [for] DCIS of a high grade. A lower grade is a little debatable. With lumpectomies, they're not generally done [for a] DCIS [diagnosis]. But with mastectomies, they are, in general.

You want to know whether special stains were done, the biomarkers. Biomarkers for invasive breast cancer are [commonly] done, [examples of those tests being] estrogen-receptor staining, progesterone-receptor staining, and HER2- or ErbB2-staining. For DCIS, it used to be that no biomarkers were done. In the last . . . ten years or so, estrogen receptor [staining] is done. Now the estrogen receptor [staining] is considered [standard] medicine . . . In the past, it was okay not to do it [for DCIS patients]. Now, if somebody comes to me for DCIS and they haven't had that done, I will [order that testing]. . . .

WOMAN:

How long ago was it that . . . for me, it's been five years since my extensive DCIS, and I had to have a mastectomy — biomarkers [were not] . . . something that was done for me, but that was five years ago. So is that something, again, another advancement that's been —

POWEL BROWN, MD, PhD:

The study that demonstrated that it was really important to do the biomarkers was published in 1999. Now, it took a while to get trickle-down, to [get] everybody [to] do it. I think in the past five years or so, it's [become] routine [testing]. What [led to that change] . . . is insurance paying for it. So that's not been ten years. . . .



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WOMAN:

I just wanted to clarify — is [biomarker testing] part of the clinical guidelines in terms of treatment in terms of DCIS?

POWEL BROWN, MD, PhD:

Absolutely.

WOMAN:

Okay.

POWEL BROWN, MD, PhD:

The NCCN [National Comprehensive Cancer Network http://www.nccn.org/professionals/physician_gls/f_guidelines.asp] guidelines, you'll see. I've read them. I knew you were going to ask me that. [Laughter] I just read them today to make sure I could answer. So 100 percent "yes." [The NCCN guidelines] say estrogen receptor [biomarker testing] should be done [for people with DCIS].

Grade — I say we want to talk a little bit about grade. The grade is pathologist's description of the appearance of the cancer cells. In this case they look at the nucleus of the cancer to see if the nucleus looks bad. A bad nucleus is a big nucleus that's got a lot of mottling. [At] Grade 1, the nucleus looks pretty [healthy and only slightly] abnormal — enough to call it cancer but not enough to say it's bad. Grade 2, it looks kind of in-between [healthy and unhealthy]. Grade 3, it's that big nucleus that's mottled and looks very bad.

There's another component the pathologist comments on, and that's comedo necrosis. Comedo necrosis just means dead cells in the middle. So remember the duct that I showed you in the beginning was filled with cells. If there's a hole in the middle, like a doughnut, where there's dead material in between that, that is comedo necrosis. Comedo necrosis is bad — it's typically associated with Grade 3 DCIS breast cancer. The reason we care about this is [because] Grade 3 DCIS is the [form of DCIS that is] most likely to come back, either with DCIS growing [back], or with [progression to] invasive breast cancer.

I [said] earlier there was something on the order of a 20 to 40 percent chance [that] people who have had DCIS [will] develop invasive breast cancer. With Grade 3 DCIS, there's about a 60 percent chance that you will have cancer come back, even with treatment. [That means] cancer [could] come back either [in the] DCIS form ... or evolving into invasive breast cancer. So it is the Grade 3 DCIS that we're most concerned about, and that [we] treat a little bit more aggressively. ...

WOMAN:

Is that more [of a concern] for people [who] have had a lumpectomy than people who have had — are we talking about recurrence in the same breast? Or does it increase your risk also of having it in the other side?

POWEL BROWN, MD, PhD:

That's a sophisticated question. The short answer is, "yes." It does increase your risk of having it come back locally at that spot. If you've had a mastectomy, there's a significant risk of Grade 3 tumors arising in the chest wall, where it was resected. But yes, just like LCIS and the others, it puts you at risk for a second independent breast cancer on the other side. So, both are true. ... if one has a recurrence of DCIS, about half the time the recurrence will be another DCIS, and about half the time it will be invasive cancer.

WOMAN:

My question is a quick one. I just wanted to know the time frame of recurrence. Is there an average time frame?

POWEL BROWN, MD, PhD:

No. It's not [as if] you're safe after two years or five years or ten years. I'll show you some graphs that show you the recurrence rate. You'll see it seems to be ... progressive ... over many years. ... Remember, if we're talking about progression to DCIS, it's not really that the original cancer recurred. It's that there might have been some DCIS cells that evolved into invasive cancer. That process ... occurs potentially over the entire ten or 20 years. ...

POWEL BROWN, MD, PhD:

... Major issues for breast cancer: Screening. I'm going to talk a little bit about how to detect DCIS, and what we should do to detect it. For anybody here, that might have been a moot point, because that might have already happened in the past. But you've got another breast, so there is a relative issue on the other side. Surgery: Should you have it, how much, and what kind? Radiation therapy: Should you have it? And if so, who should have it? Hormonal therapy, the antiestrogens, tamoxifen or the aromatase inhibitors: Should you get that? Or is there something else that you should get? And that speaks to the question about HER2 status.

Let's start with screening. [One] screening [option] is a mammogram. [In the United States, the recommendations are for] everybody over the age of 40, [even] without a family history [of

breast cancer], to get an annual mammogram. If you have a family history [of breast cancer], it might be earlier than that. This is a digital mammogram done at our [cancer] center. ... the white is the dense breast tissue typically seen in young women. The dark is the fat of the breast, or the stromal tissue. And [in the] ... outline. There are calcifications on this mammogram. ... It's difficult to see [on this mammogram], and it's difficult to see for the radiologist in young women who have premenopausal, dense breasts. ...

So, as you know, they then squash you with the magnification views. [Laughter] And then you can begin to see the dots. ... It kind of looks like salt. And these are the calcifications that show up on a mammogram. ... Big chunky calcifications are ... usually benign and not too worrisome. Little tiny calcifications are more worrisome. And the most worrisome of all are what is called pleomorphic, or different sizes. So, multiple, different sized, tiny little calcifications all in a cluster and pointing different ways is almost diagnostically cancer. So that's what we look for. And this one here is a real chunky one, but there are multiple little ones in here, and this is DCIS.

One of the problems, particularly in young women, is the difficulty with mammograms — seeing through that dense, white tissue. [To be able to see through the dense tissue better,] we have MRIs [magnetic resonance imaging]. So it may be that your doctor would order MRI now. In the past, we didn't do MRIs that frequently. Now, virtually all patients who have had newly diagnosed DCIS in the past year get an MRI.

If you've had DCIS diagnosed [longer ago, you probably didn't [have an MRI]. But you can see why [it would be done]. There's [a] question [about] the extent of the disease [and an MRI can provide some information to make that judgment-call]. ...

But here's the MRI. ... this white thing is all DCIS. It's involving at least half the breast on that side. [Here is where the MRI shows something that was not apparent in the] mammogram. [This is an example of where] ... the MRI can help, particularly in young premenopausal women who have dense breast tissue. That might be very helpful to both detect it, but also plan your surgery, because on the first mammogram it looked like we could have done a lumpectomy. [But the MRI shows that] half the breast [is] involved, [so] we can't do [just] a lumpectomy. Mastectomy is the only choice for that person.



By the way, the MRI is done bilaterally, so you also have a chance to see if there's a second cancer, because these women are at risk of another cancer. If you're young, [and] you have a family history [of breast cancer], you might be in a genetic risk [category] for getting multiple cancers. . . . So that [second cancer] can show up on the MRI.

Breast MRIs [are] now much more commonly used [to diagnose cancer]. [They are] being used routinely in women with . . . new diagnos[es] of DCIS, [and are] used frequently in a new diagnosis of invasive breast cancer. [MRIs are] also used in women who don't have . . . cancer, but who are at high risk [for cancer]. For women with DCIS or invasive breast cancer, it's used to detect additional cancers that might affect [a treatment plan]. And in the case of DCIS, it's often used to define the extent of DCIS, to help plan surgical therapy.

In women who don't have cancer but are at high risk of it — those people include BRCA1 or [BRCA]2 mutation carriers, women with that other CIS lesion, the lobular carcinoma in situ, or women that have been calculated to have [a] greater than a 20 percent lifetime risk of breast cancer by the Gail Model, or other models that can predict the likelihood of breast cancer — these women would be candidates for breast MRI as a screening test . . . in conjunction with mammogram. Right now, the recommendation is [for] annual [screenings]. I'm wondering if the insurance companies are going to keep letting us do . . . breast MRIs [annually]. Because mammograms, at least in Houston, are costing anywhere from about \$100 to \$300 [each], depending on where you go, [and breast] MRIs cost around \$3,000 to \$4,000. So obviously that's a burden on our healthcare system.

WOMAN:

So, are you saying [screenings should be done] for follow-up, too . . . yearly after [cancer treatment] —

POWEL BROWN, MD, PhD:

For whom?

WOMAN:

Well, depends. I guess for people who have already had [the mammogram and have] had cancer.

POWEL BROWN, MD, PhD:

I told you who should get annual mammograms — very high-risk people, [regardless of whether they have ever been

diagnosed with cancer]. So the question is: Should people who have had one cancer get annual MRIs? The answer . . . really depends on other factors. In general, the answer is "no." . . . [But] that does produce somewhat of a paradox. [As for] everybody who's had cancer, I am not standing up here saying you need an annual breast MRI. On the other hand, if you have other risk factors, if you've had LCIS, if you have a strong family history, if you know you have a BRCA1 or [BRCA]2 mutation, then the answer would be "yes." MRI is particularly useful . . . [in] detect[ing] cancer, or gaug[ing] the degree of cancer in young women who have . . . dense breast tissue already.

Many people say, "Should we just do screening MRIs?" Or, "Should MRI replace mammogram?" Or, "Why do I have to do both?" [The viewing of the two test results that we did today] explains it. First, this shows the frequency that the MRI or the mammogram detected the cancer, and in this case, the Grade I and [Grade] 2 DCISs, and in this case the Grade 3 DCISs. . . .

In this case, MRI and mammogram both showed the cancer. This is in terms of diagnostic screening. So, about half the time in [the cases of] low-grade disease, either the MRI or the mammogram may be sufficient to see it. About 13 percent of the time, only the mammogram sees it. So they're complementary tests. It's not that the MRI is better than the mammogram. It's that they see different things. Mammograms see calcifications better than MRIs do. So, 13 percent of the time, you'll only see it on the mammogram; and about 37 percent of the time, you'll only see it on the MRI, in low-grade disease. So I'll go over that again. It's a little confusing.

Half the time, both of them show [if cancer is present]. But about, what, a tenth, a little more than a tenth of the time, only the mammogram shows it. That's low-grade disease. And the reason only the mammogram shows it is because low-grade disease is associated with calcifications. High-grade disease, on the other hand, is less frequently associated with calcifications. So what you see with high-grade disease is, again, about half the time, high-grade DCIS is found both with the mammogram and with the MRI. But the other half of the time, the mammogram misses it and only the MRI sees it. So, stated again, in high-grade DCIS, the mammogram is not as good as the MRI in picking that up. So most of you guys, if you've had DCIS, probably had it picked up by virtue of a mammogram showing calcifications.

And then, that usually means that it was low-grade disease.

I will say one other thing: . . . before mammograms were used frequently, DCIS was picked up by palpation, a mass. And [DCIS does] . . . form masses. But [not in its low-grade form] . . . But there was more high-grade disease then, too, because we weren't [detecting] the low-grade disease with mammograms. So, high-grade disease can form calcifications. As you can see here, half of the time both mammogram and MRI will see it. But on high-grade disease, it may not have calcifications.

WOMAN:

My question is about ultrasound. . . . I have bilateral Grade I [DCIS].

POWEL BROWN, MD, PhD:

Only DCIS, no invasive cancer at all?

WOMAN:

Both. DCIS on the left and invasive on the right.

POWEL BROWN, MD, PhD:

The invasive on the right's a whole different story, but okay, go ahead.

WOMAN:

The ultrasound: Is that something — that was what was used to detect, you know, on both sides.

POWEL BROWN, MD, PhD:

It probably wasn't used to initially detect it. Did you have it picked up on one of the other modalities, and they did ultrasound after that?

WOMAN:

No, ultrasound first, and then later on I had mammogram and MRI.

POWEL BROWN, MD, PhD:

Why did they do the ultrasound?

WOMAN:

That was what they used? I don't know. I don't know.

POWEL BROWN, MD, PhD:

So you didn't have any palpable thing? You didn't have any mass or any problem? You just said, "I need an ultrasound"?

WOMAN:

No, I felt it.

POWEL BROWN, MD, PhD:

Ah.



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WOMAN:

I felt it on the right, in here.

POWEL BROWN, MD, PhD:

Well, there you go. So, yes, if you feel a mass, particularly in a premenopausal woman, the first step will be ultrasound —

WOMAN:

Okay.

POWEL BROWN, MD, PhD:

Because the doctors are thinking, “Well, could this be a cyst?” which is common in premenopausal women. So they’ll do an ultrasound to look for a cyst. Was it cystic or solid?

WOMAN:

Cystic.

POWEL BROWN, MD, PhD:

Hmm. Okay. They will always — or I guess almost always — do a mammogram after that, just to be complete. So it’s a cyst. They saw it on an ultrasound. Then they did the mammogram, and the mammogram showed —

WOMAN:

That it was cancerous.

POWEL BROWN, MD, PhD:

Did it show calcifications?

WOMAN:

I’m not sure. So they followed it up with MRI, because they said it was dense, dense tissue.

POWEL BROWN, MD, PhD:

Okay, I’m not sure of the whole situation. But ultrasound is used ... to diagnose cysts, and determine whether something is cystic or solid. It’s also used in cases, if you did the mammogram first and you saw calcifications, they’ll also frequently do ultrasound to see if [the calcifications are] seen on the ultrasound, because [the ultrasound] can facilitate biopsy. They can do the biopsy under ultrasound guidance.

WOMAN:

That’s what they did.

POWEL BROWN, MD, PhD:

If they can’t see it on ultrasound, and it’s only seen on mammogram, they have to do the biopsy under stereotactic guidance with the mammogram. If they only see [dense breast tissue] on MRI ... [and] ... don’t see it on ultrasound ... and then you do the other mammogram and the mammogram’s negative, the only way to biopsy that is with MRI-guided biopsy. MRI-guided

biopsy is not a simple thing. Many, many places can’t do it or don’t do it yet. You can’t use a metal needle because of the magnet. You’ve got to use a plastic needle. It’s very lengthy and time-consuming and noisy with that MRI. So the radiologists don’t want to do [MRI-guided biopsies]. They try to ... use the ultrasound to see the lesion, so it will be easier to biopsy. But sometimes you have to do an MRI-guided biopsy, particularly with high-grade disease.

WOMAN:

Regarding the needle-guided biopsy through ultrasound, I had that done and it came [out] negative. So if somebody [were] to ask me my opinion, I would just — if they did develop some kind of lump, like I did, [what] would ... be the best way to just get it out? And then — only then will they really know if it’s cancerous or not? I mean, what would I have ... done? I didn’t do a second opinion because they said, “Oh, you know, it’s not cancerous.”

POWEL BROWN, MD, PhD:

So, typically we recommend needle biopsy, not excisional surgical biopsy. In a good center, needle biopsy should be over 90 percent predictive. Now, there will be mistakes along the way. If you [biopsy] thousands of people, there will be things that are missed or cases that might be false negatives. If it’s positive, it clearly needs further surgery. But most centers are not recommending surgical excision as the first step. Although some lesions that are very difficult to reach by stereotactic guidance — where they can’t see it with the ultrasound or something — they might do surgical excision.

So, to state that again, most places won’t recommend surgical excision [as a first step] ... but [will instead recommend a] core needle biopsy. One of the reasons for that is because you can plan much better [for] cancer surgery with [results from] the needle, [and better determine which surgery] you ... want ... as opposed to doing the wire localization and excision. If they [start with the excision] ... and they find it’s cancer, they’ve already taken a chunk of breast out. The cosmetic result [then creates a need for] further surgical planning [that possibly could have been avoided]. ...

But ultimately ... I would recommend ... go to a ... good center and ... trust them to make a good call ... [Next question?] ...

WOMAN:

... I had [a] bilateral mastectomy last year due to DCIS in both breasts. ... My question is that I’ve lost both the breasts, and I’ve had tissue flap reconstruction, and I’m not doing very well. It was pain that led to the diagnosis, not my mammogram 90 days before the diagnosis.

So the left mass was eight centimeters. It was big. It was almost the size of my natural breast. I didn’t know to expect pain after the bilateral mastectomy. It’s been a year and a half, and I still have what my intellect tells me is the identical character of pain that led to the diagnosis of my third cancer, which was breast cancer. I managed to get through brain tumor diagnosis and everything else, but now I cannot — the hamster in my brain will not get off the treadmill that he’s on, that says, “Your cancer wouldn’t have been detected without pain.” The pain’s not gone. They’ve told me the pain can be managed with Neurontin, but I don’t want to cover up pain ... if —

... My question has to do more with the 2 percent of women. What happens when — you know, they say they’re 98 percent sure that all the [cancerous tissue was removed] — but the margin was very narrow because the mass was so large. So you understand me, I guess.

POWEL BROWN, MD, PhD:

I do, yeah. So, that’s a horrible story, and I’m sorry you’re going through that. ... I don’t know the whole case, so I’m not going to say specifically what you should do. We can talk later, if you’d like.

But, I think what you’re saying is you’ve received what most doctors would consider the most appropriate therapy. In part because you detected this with [a] sensation of pain, and now you’ve got pain again, [so] you’re terrified that there’s still cancer there. You can’t distinguish whether it’s cancer, or pain from the surgery. You may be implying that your doctors are telling you, “Don’t worry about it. It’s not there.” That’s a problem. Nothing any doctor can say is going to stop you from worrying.

There are things [you can] do about that. There are cases — and I’m not suggesting this for you — but I certainly have patients in my practice [who] are so concerned about the possibility of recurrence, that they will have mastectomies when there’s no lesion there. Or they’ll have additional surgery to absolutely remove all the tissue, more over concern and just absolute inability to live with



the concern [that the cancer] could come back. That sounds similar to what you're going through. I don't think there's an easy answer for that, and certainly not one I can give you in two minutes here. But I understand that there's no way you can distinguish [whether the pain is cancer], and you're terrified because you've had ... the experience of having pain and having it be cancer. So of course you're concerned that pain might be cancer again.

WOMAN:

If you're getting too many question[s] and you can keep going on —

POWEL BROWN, MD, PhD:

Well, I guess I should take a look at the time, but I don't mind the questions. I will state that I'm not trying to be [a personal] physician [to each of you]. So I may sort of bug off specific recommendations.

WOMAN:

I heard you speak earlier about a needle biopsy, and I just want to make sure I understand that that's not medically synonymous with the fine needle aspiration. In my experience, I [felt] my lump. I had an ultrasound because it was believed to be cystic. At the time I was 24. So [a cyst] was perhaps the most obvious ... culprit, so to speak. [After I felt the lump] ... my surgeon undertook a fine needle aspiration to, I guess, test the fluids. Only after the results came back did I have a biopsy to remove the mass completely. At the time [I had the biopsy] because [the lump] was there and it was bothering me. Nobody knew what it was. [We later learned] ... it was DCIS. So I'm just trying to make sure I can appreciate your indication of a needle biopsy versus a fine needle aspiration, which was my experience.

POWEL BROWN, MD, PhD:

That's a very important point to bring up. Thank you. ... There are two types of needle biopsies: the fine needle, which is generally not used for diagnosis of breast cancer, and a core needle, which is used when ... appropriate.

First of [all], stereotactic biopsies that I was referring to [earlier] are core needle biopsies, where they take a chunk of tissue that the pathologist gets to look at. That's critical. You need a core needle. An aspiration biopsy or fine needle biopsy, it would be inappropriate in that setting.

Now, on the other hand, if they see a cyst and they want to drain a cyst, aspiration biopsy with a fine needle is appropriate. The recommendations

are that if it recurs in a young woman with no other abnormality, you can drain it again, and if it keeps recurring, one might excise it. If somebody has a strong family history or there are other reasons you're at high risk for cancer, then you might be a little more aggressive in that case. ...

So, we were talking about screening and diagnosis. Mammograms are still used to screen for breast cancer, and they are able to detect low-grade DCIS with calcifications and some high-grade cancers. MRI may be more sensitive than mammography in diagnosing DCIS, particularly those high-grade ones, so that MRI may be used more often in the future.

Mammogram plus MRI is the appropriate screen in the high-risk individual, not one or the other. Because we're here at the [Annual Conference for Young Women Affected by Breast Cancer], young women are particular candidates for MRI because of the dense breast tissue. And I already told you that MRI is often done at times at the diagnosis of DCIS to rule out a contralateral breast cancer.

... Let's talk about treatment, now that one has it. What does one do? The goal of the treatment, it's a little different than invasive cancer. The goal of treatment here is to prevent it from progressing to invasive cancer. So the DCIS itself is not the dangerous culprit. It's what it might turn into.

Now, surgery is the mainstay, either lumpectomy or mastectomy. I already told you that you might need extra surgery if the margins are positive. Radiation therapy is a discussion, particularly if you have a lumpectomy. The standard of care is to recommend radiation. However, almost every one of my patients doesn't want radiation, and they try to talk me out of recommending it. [Laughter] In fact, there are situations where some physicians will recommend that you don't — well, [where some physicians] will say, "You don't need radiation." I'm going to show you a little data about that, and we may talk about that. But for most DCIS, if you have a lumpectomy you should have radiation.

Hormonal therapy can be used. If you're estrogen-receptor positive in the DCIS cells, then tamoxifen is a useful agent. It reduces the risk of [a] DCIS [recurrence] by 50 percent. What about the new medicines, aromatase inhibitors? They're used only in postmenopausal women, or women who have been rendered postmenopausal with medications or surgery. They're not used for DCIS

at all right now. They [a]re in clinical trial [for use in DCIS], though. ...

Chemotherapy: Good news is nobody gives chemotherapy for DCIS. So you would not get chemotherapy recommended to you for that.

What about HER2 positive DCIS? ... We don't do anything special [in terms of treatment] for [HER2 positive DCIS] yet, and therefore we don't test for HER2 routinely. We'll talk more about that, though. What about ER negative DCIS? Well, there's nothing for ER negative DCIS, just like there's no targeted therapy for ER negative invasive breast cancer. So, for ER negative DCIS, which is typically the high-grade kind [of DCIS], we really don't do anything other than the surgery, [such as a] ... lumpectomy, then radiation. Maybe we should, though. ...

One last thing: genetic testing. You might be a candidate for genetic testing ... if you're young and you have DCIS; or if you have multiple cancers like somebody in the audience mentioned; or if you're Ashkenazi Jewish and have DCIS at a young age. The most common genes tested are BRCA1 and [BRCA]2, but there are others. If you test positive for one of those breast cancer-causing genes, most of your physicians will at least discuss the possibility of bilateral mastectomy with you. You might choose to have a mastectomy for the DCIS side and a prophylactic mastectomy for the other side.

I'll tell you, [in] my practice I like to say I never recommend mastectomy — bilateral mastectomies — prophylactically. I discuss it with the women, and I give them the information. Far be it from me to tell you to have surgery on unaffected breasts. But it is medically appropriate and a very reasonable option for some [women].

WOMAN:

With [use of] tamoxifen — what's the percentage of recurrence?

POWEL BROWN, MD, PhD:

I'll show you the graphs. [Laughter]

So, DCIS is a marker for being at high risk to develop invasive cancer. The diagnosis and treatment are critical ... to rule out concurrent presence of invasive cancer, and that's part of the deal. We want to do surgery to make sure it's not something worse, but also to prevent the development of progression. So we want to get the DCIS out of there. That's the surgical plan.

It's managed fairly like we manage LCIS or ADH, although those don't typically get radiation.



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So we do manage those as high-risk lesions. No radiation, though.

Surgery: The major decisions in surgery are whether you should get the lumpectomy or whether you should get the mastectomy. That depends on a lot of things. It depends on the extent of these. It's like that picture I showed you that involved the whole breast, [in a situation that was] ... pretty obvious ... It depends on location of the DCIS. If it's right under the nipple complex, and to resect that [requires removal of] the nipple and the areola, most of the surgeons will tell you that they can't get a good cosmetic appearance after that lumpectomy. So they'll probably say that has to have a mastectomy. If it's a relatively moderate sized DCIS, but you're a very small-breasted woman, a mastectomy may be the only choice just from a cosmetic reason alone. ...

Family history: BRCA1 mutation might cause one to have a mastectomy over the lumpectomy. It might also cause you to have a prophylactic bilateral mastectomy.

... Radiation [is] typically offered if [a] lumpectomy is done. Sentinel lymph node dissection can be done. ... [It's] generally not done with lumpectomy for DCIS, [but it is] considered, particularly if you have a mastectomy.

[The decision of whether or not] ... you should have radiation ... usually takes about 30 minutes of my visit with [a woman]. Because I say they should have radiation, and they say "no," they don't want radiation. I have to tell them why they should have radiation, and they tell me they still don't want radiation. [Laughter] And then I say, "Go talk to the radiation oncologist." [Laughter] It depends on [whether] you had a lumpectomy or mastectomy. We generally won't recommend radiation after ... a mastectomy. The only way you'll get radiation after a mastectomy for DCIS is if ... they find invasive cancer and it's involving the chest wall, or if they find invasive cancer and it's spread to the lymph nodes ... then we'll recommend radiation. But generally women who have mastectomy for DCIS don't have to undergo radiation.

That last line is the problem. Some women treated with lumpectomy may not need radiation. And there's a whole camp of folks in California [who follow criteria developed by] Dr. Silverstein ... called the Van Nuys [Prognostic] Index, which tries to index the DCIS lesions to those that are the least likely to come back. He [contends that] people [with the lower-risk lesions] don't need

radiation. They're typically the Grade I DCISs that have a very small size [lesion] and have big margins, free margins. In those people it might be okay to not give radiation.

On the other hand, the NSABP [http://www.nsabp.pitt.edu] clinical trials group has tested this and found that [all people with DCIS], low-grade and high-grade individuals, benefit from radiation equally. But it's just that low-grade [DCIS] has a lower chance of coming back at all. So you're cutting the risk of those people coming back, but they had a low rate anyway. So the absolute benefit isn't as big.

So there is somewhat of a controversy here. Should we ever say it's okay for some people not to have radiation? Some physicians will say, yeah. ... Radiation is generally the standard-of-care, but for the best-prognosis lesions, you can probably talk me out of it. ...

Here's some of the data. These are four large studies of DCIS patients that were either treated with ... surgery alone or [surgery plus] radiation. And all these people got lumpectom[ies], not mastectom[ies]. You can see the follow-up is 12 years, ten years, ten years or four years, so some of these are pretty long. With surgery [alone], there was somewhere between a 25 and 30 percent chance of having the cancer come back — the recurrence, local recurrence, not distant spread. But you can see those people who got radiation [plus surgery], every one of these cuts it by about 50 percent. So radiation did reduce the risk of the cancer coming back by 50 percent. That's why we recommend it. If you look at the different grades ... it will show you that everybody at every grade benefits [from adding radiation to surgery]. It's just at the lower grades, [DCIS recurrence is low after surgical removal of cancerous tissue anyway] ... so maybe for them it's okay to avoid radiation. But [all grades] appear to benefit. ...

WOMAN:

These are all lumpectomies?

POWEL BROWN, MD, PhD:

Yes, not mastectomies.

Hormonal therapy: Should you take hormonal therapy? It depends on the status of the estrogen receptor in the DCIS. If it's [a form of] DCIS that's estrogen-receptor positive, we often recommend tamoxifen. It also kind of depends on the grade ... You may be somebody that says, "I'm just not taking tamoxifen. I've heard all about tamoxifen and I'm not taking it." Well, okay.

[Laughter] On the other hand, tamoxifen will reduce the risk of the cancer coming back by 50 percent, just like those other numbers I showed you. For ER negative DCIS, they're the ones that are more likely to recur, and tamoxifen doesn't help them. ... I told you aromatase inhibitors might be useful for this purpose. It's in clinical trial, being tested now in Europe. But they're not done. So we don't give aromatase inhibitors in this setting. Questions about tamoxifen?

WOMAN:

I'm one of those [people who is] ... not going to take [tamoxifen]. That's my personal decision, because they told me it's not guaranteed that [the cancer is] not going to come back. I weighed the side effects and how it's going to affect my lifestyle, so [not taking tamoxifen] was my decision. But there are other alternative [medications and therapies] that I would think would increase your chances of not having it again.

POWEL BROWN, MD, PhD:

I'll speak to that. This sort of gets into the realm of prevention also. There are lots of ... alternative medicines and other therapies. You heard earlier on that I did a clinical trial with a vitamin A derivative in this setting. In addition, soy products are touted in this regard, that they might be useful. You may have other herbal agents that are potentially useful, other CAM [complementary and alternative medicine] agents. The fact is none of those agents have been anywhere close to ... as effective as tamoxifen. Tamoxifen reduces the risk of the cancer coming back — whether it's prevention for people who are high risk or whether it's DCIS — by 50 percent. Exercise might reduce [recurrence], but ... only ... [by about] 5 or 10 percent. Resveratrol [an agent that occurs naturally in] red wine [that is also available as a dietary supplement] might affect it, but it's nowhere close to 10 or 20 percent. Soy: nowhere close.

So, unfortunately, maybe, tamoxifen is the most [effective] agent. ... In my opinion, you won't get anywhere close to that degree of reduction in your risk of recurrence with any other available therapy.

WOMAN:

With regard to risk reduction and tamoxifen, are you saying that the 50 percent risk reduction is if you take tamoxifen for — I believe it's a recommended five-year regimen. I personally took it for two and a half of the five years, and then the



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side effects were way too extreme [for me]. [If I took it for half the recommended regimen], does that mean ... half of the risk reduction?

POWEL BROWN, MD, PhD:

Yeah. It does look like it's a linear curve, and that if you take it shorter time you have that proportional amount. ... I would predict that you'd have a reduction in the risk — individually, you either have 100 percent or a 0 percent. So you either don't get cancer or you do. [Laughter] But on a population level, on the population level, somebody taking two and a half years of tamoxifen, we'd expect about a 25 percent reduction in risk.

WOMAN:

I'm ER positive. Is soy really something good for me to take, and soy and flaxseed, because they have estrogen in them, too.

POWEL BROWN, MD, PhD:

That's a really good question. And it opens up a whole can of worms that I would like to talk about. But maybe we can put it off to the end of this [program], because it's a complicated answer. Soy is okay for some and not for others. Right? That's the short answer.

WOMAN:

I had that question, too. But I also wanted to know your opinion. Do you think that tamoxifen can cause joint pain? My oncologist says no. [But] I've heard mixed reviews. I have extreme joint pain, and she disagrees with me [on the cause of the pain].

POWEL BROWN, MD, PhD:

Well, I'll tell you, the aromatase inhibitors —

WOMAN:

I just want your personal opinion. I won't hold you to it.

POWEL BROWN, MD, PhD:

The aromatase inhibitors, the other ones, definitely cause joint pain and bone pain, no question about it. Tamoxifen joint pain is not a common side effect.

WOMAN:

Is that my menopausal, like, arthritis that's coming up?

POWEL BROWN, MD, PhD:

Yeah. People who are perimenopausal or postmenopausal can have a lot of other symptoms, too. It's hard to distinguish what's from the medicine and what's from other things. I don't know. ...

I can't say for you. [Joint pain] is not a common side effect of tamoxifen, we'll put it that way ...

WOMAN:

I guess it's just my old woman in a young person's body.

POWEL BROWN, MD, PhD:

Yes.

WOMAN:

They couldn't give me a lot of definitive [information], I think, because there are so few women who are young and have not had chemo [as part of their treatment], as far as the side effects [of tamoxifen on] fertility ... My oncologist told me they were giving tamoxifen initially to enhance fertility. But she also says it can throw me into premature menopause. So I'm wondering, like —

POWEL BROWN, MD, PhD:

So, did you have invasive cancer or DCIS?

WOMAN:

I had DCIS.

POWEL BROWN, MD, PhD:

Right, so not invasive cancer.

WOMAN:

Not invasive cancer. But basically she was saying, "I can't really tell you what it would do to your fertility because we don't have enough studies in women in your specific situation that have not had chemo" ...

POWEL BROWN, MD, PhD:

I'm not sure I'd answer it that way. I've given tamoxifen to plenty of young women, including ... women [who] are potentially fertile. ... [For] ... people who are interested in childbearing, I don't use it, and it's actually a potential teratogen that can affect the fetus. So you don't want tamoxifen around if you're trying to get pregnant, period.

Now, initially it was tested as a potential fertility drug, because it can stimulate ovulation. There are a lot better drugs ... for that now, so you don't want to use tamoxifen for [fertility]. So if you want to get pregnant, no tamoxifen, even if you have breast cancer.

... if you had invasive breast cancer and you're treating with chemotherapy and it was really high stage and ER positive, I might tell you to use tamoxifen and then we'll talk about fertility in ten years or something. There are special settings. But, in general, I wouldn't use tamoxifen in that case.

And tamoxifen doesn't generally throw you into early menopause. It gives you menopausal symptoms, but it generally doesn't stop your periods. ...

WOMAN:

I'm not sure I understood your answer. Did you say if you're planning to get pregnant ever, don't use tamoxifen? Or ... while you're on tamoxifen don't try to get pregnant?

POWEL BROWN, MD, PhD:

Certainly the latter. If you want to get pregnant, don't take tamoxifen at that time. The other one is kind of more dependent on timing and when you want to be pregnant and things like that. I can't give you a general answer. Everybody's different in that case. But you've got to be careful. There might be better choices than using tamoxifen if you're planning on pregnancy. And it would depend on if tamoxifen is being used to treat invasive cancer, or if tamoxifen is used for prevention. In general, although I give things to prevent breast cancer to a lot of people, I'm a bit reluctant to give tamoxifen to extremely young women who are at high risk, but who are wanting to get pregnant in the next five to eight years.

... You've got to take tamoxifen for five years, ... and tamoxifen has a long half life, by the way. It will hang out at least for a few months after — well, two to six weeks after stopping. ...

WOMAN:

The 50 percent reduction in recurrence, that's based on years of study I presume, right? And the thing is that my doctor said [tamoxifen has] been around for many years, and that's ... [why it's considered] very effective. But I was thinking most of those women that probably were [using] ... tamoxifen were not premenopausal. Did they differentiate how it affects a woman in her 30s or her 20s, versus somebody who's in their 50s or 60s? Somebody's in their 50s, 60s may have a different hormonal makeup than somebody's in their 20s or 30s, and so the [effectiveness might differ].

POWEL BROWN, MD, PhD:

Your point is well taken, that both the effectiveness and the side-effects profile are different in postmenopausal [versus] premenopausal women. ... I can tell you at the dose of 20 milligrams a day of tamoxifen — [and that's] a pretty hefty dose of tamoxifen —



it is effective in premenopausal women. So you don't need to worry that because you're premenopausal it won't work. It blocks the effects of estrogen on the breast tissue.

On the other hand, it doesn't suppress your estrogen level as a premenopausal person. You still have circulating estrogen. Therefore, premenopausal women taking tamoxifen don't have as many of the postmenopausal side effects that postmenopausal [women taking tamoxifen] do. So, premenopausal women tolerate tamoxifen much better than postmenopausal women. Postmenopausal women have a low estrogen level already. They may already have some hot flashes, and tamoxifen often makes those much worse.

... there have been fewer premenopausal women given tamoxifen, but now ... that we use it for prevention purposes, many, many more [premenopausal women] are [taking it]. In general, premenopausal women are much more able to tolerate the medicine. They have fewer hot flashes, and they're in general in better health. So they're not going to have as many frequent problems with blood clots and other things. They also generally aren't going to get uterine cancer from tamoxifen, because they slough their uterine lining each month. And thus it is a much safer drug, and better tolerated in a premenopausal setting, than it is in the postmenopausal setting.

WOMAN:

... If you do not take tamoxifen right after the time of diagnosis because either you didn't want to take it then, or the whole pregnancy thing, is there an advantage to taking it later on?

POWEL BROWN, MD, PhD:

... the medical literature recommends beginning tamoxifen within a certain frame of your initial diagnosis, and generally that's within a couple of months. That's for reduction of recurrence. But you're also talking about this as a high-risk lesion, putting you at risk for another cancer. Tamoxifen, at any time, should work for that. So I think it [would be advisable] to use tamoxifen even years [after a diagnosis]. But [there should be] a discussion and reassessment of your risk-benefit ratio and all that. It's a more complicated question that just saying, "yes." But it might be appropriate to use tamoxifen years after your original diagnosis, particularly if you have other risk factors.

WOMAN:

What about going off [tamoxifen], being on it for a couple of years, and then taking a "baby break" or something. Or maybe waiting a few years before trying to get pregnant, as you're recommending, and then going back on? ...

POWEL BROWN, MD, PhD:

So, [a] baby break [i]s okay. I mean — no, well [laughter] [a] small break, okay, meaning a month or two. That's commonly done. If you're taking a break to have your children, I would say [you should wait until you're] ... done [with] tamoxifen ... Let me keep going. You'll have lots of other questions along the way.

You asked about the length of follow-up and how long tamoxifen has been studied. These are the data from the NSABP [National Surgical Adjuvant Breast and Bowel Project; http://www.nsabp.pitt.edu/Abstract_59.asp] trials, comparing people that either did or didn't take tamoxifen, placebo-controlled trials, for those who had breast cancer come back. In this trial everybody got radiation. Everybody got [a] lumpectomy, and everybody got radiation. The dotted line shows if you take placebo over five years, this is your risk of having the cancer come back or developing a new one. [The risk is] ... about 14 or 15 percent. Without the radiation, that would be 30 percent. Note this [was] done in 1999, so [tamoxifen has] been around, and these results have been known for a while. This stuff has been followed for many, many years. So this is pretty sure. There have been meta-analyses of [tamoxifen use, drawing on the experiences of] thousands of women. So [the effectiveness of tamoxifen] is not in contention.

You can see that it decreases the risk of [recurrence for both] invasive [and] noninvasive cancer. ... It decreases that risk by about 50 percent. [That is] about equal [to] the number of people [who do have a recurrence with use of tamoxifen]. ... So about half and half. So, tamoxifen does reduce one's risk of having the cancer come back by about 50 percent.

This I threw in just to show you the effect of radiation. So, the dotted line here is from an earlier study done in the early 1990s, the B-17 trial [http://www.nsabp.pitt.edu/Abstract_24.asp]. That's what you do if you have no radiation. There's about a 25 percent risk of having breast cancer come back [in five years] after DCIS, [and the standard treatment for DCIS]. The line keeps

going up, so that's how you get that 20 to 40 percent lifetime risk. If you get radiation, radiation cuts your risk down to here. That's the effect of radiation. That's why I tell everybody it's useful after lumpectomy. ... This is the effect of tamoxifen. So radiation plus tamoxifen is the most effective way ... [to treat] estrogen-receptor positive DCIS. And all these people [Editor's Note: pointing to slide] had estrogen-receptor positive DCIS. If you have estrogen-receptor negative DCIS, then your line comes to here with radiation ... And, again, [radiation] reduces [the risk of] invasive breast cancer and noninvasive breast cancer.

Moving ahead [to] ... the decisions and the treatment: For small, Grade 1 DCISs, [the decisions come down to] lumpectomy or radiation or mastectomy. And you could try to talk your doctor out of the radiation if it's a real small DCIS. But, Grade 2 or Grade 3 DCISs really should be treated with lumpectomy and radiation, or mastectomy. ER positive DCIS is often treated with tamoxifen. ER negative is not.

[Someone] asked about HER2 positive DCIS. There are clinical trials testing anti-HER2 agents in DCIS. One of these was done at M. D. Anderson [Cancer Center in Houston, Texas; <http://www.mdanderson.org>]. Dr. [Henry M.] Kuerer did this study with Herceptin [<http://utmsi01a.mdacc.tmc.edu/dept/prot/clinicaltrials/swp.nsf/Index/2004-0701>]. That's the drug that's commonly used for HER2 positive breast cancer. He tested it in DCIS. The results of this trial are not out yet. ... He took people [who] had newly diagnosed DCIS, treated them with a single dose of Herceptin, and asked what [that single dose did] ... when [participants] ... [were given an] excisional biopsy. So these are people that had a stereotactic biopsy first and then an excisional biopsy. He has completed the trial, and he's doing this biomarker analysis to see what effect the Herceptin had. I don't know the answer, but it's beginning to look like people with ER negative cancer that's ErbB-2 [HER2] positive, might get additional therapy also.

We're running another trial on the same idea using a pill. The pill is lapatinib, ... an oral drug you take once a day. It inhibits the HER2 protein from sending a growth signal to the breast cell. It also inhibits the EGFR [epidermal growth factor receptor, also known as HER1] protein from doing the same thing. It's called a dual kinase inhibitor. It's now FDA approved for treating patients with HER2 positive metastatic breast



cancer. So it's not an experimental drug by any means. It's also in phase III trials, testing for early-stage breast cancers that are HER2 positive. Might this work either instead of Herceptin or in addition to Herceptin? That's being tested in a clinical trial right now.

We are testing whether it might be useful in DCIS. So this is the description of that trial — an ongoing, open trial [<http://www.clinicaltrials.gov/ct2/show/study/NCT00570453?term=lapatinib+%2B+DCIS+%2B+intraductal&rank=1>]. Women who have newly diagnosed HER2 positive DCIS, or EGFR positive DCIS, they have [a] stereotactic biopsy just like in that other trial. They receive one of three doses of lapatinib or placebo. We're testing the effects of lapatinib, but we're also asking, "Could we use a lower dose than the standard dose?" The standard dose is [a] high dose — 1,500 milligrams. We're decreasing the dose to see if it can be [used with the participant experiencing] even less side effects and [the medication] still [being] effective. The women then go for excisional surgery . . . Then we look at whether there's DCIS left there — whether the cells have been killed or . . . the growth of the cells is reduced. That's being done at a bunch of different institutions now. It's open in Houston. It's not open in Dallas. I should talk to people up here. [Laughter] But it's open in a variety of places, at Harvard [s Dana-Farber Medical Center], at Georgetown [University Hospital] and Walter Reed [Army Medical Center] . . . and [Baylor College of Medicine].

. . . The idea is DCIS is intraductal — it's within the duct. Could we treat within the duct? It's potentially possible to do that by injecting into the nipple. One can cannulate [insert a small tube into] the nipple. If you've heard about ductal lavage [washing of the duct] — instead of lavaging, taking . . . out or [inserting] fluid . . . Theoretically you could squirt chemotherapy into [the duct to] kill the DCIS cells. That is being tested in a clinical trial as well [Editor's Note: Some information on one trial <http://www.clinicaltrials.gov/ct2/show/NCT00671476?term=DCIS+chemotherapy+cannulate&rank=1>] This shows someone who's had that procedure, and they injected dye, and then they did a mastectomy for cancer. You can see the dye can define the ducts themselves. Then when you get the tissue, you can see the dye in the duct. . . One of the problems is you have about seven to eight ducts per nipple, and it's difficult to cannulate

every one of those. But that's a technical problem that's being worked on.

There is a trial right now using this process of intraductal injection of chemotherapy, carboplatin, in women who have DCIS [<http://www.clinicaltrials.gov/ct2/show/study/NCT00669747?term=NCT00669747&rank=1>] and asking whether it will kill the duct cells. This is not taking chemotherapy systemically. It's just in the area of the duct. So it virtually has no side effects, other than the discomfort of cannulating the nipple, which is a little uncomfortable. And that's ongoing at M. D Anderson [Cancer Center], Oklahoma [University Medical Center] and several other places around the country.

What you guys may care more about is what you do after the diagnosis. How should you be screened? What can you do other than tamoxifen to reduce the risk of cancer coming back . . . ? If there's remaining breast tissue at risk, meaning you didn't get the bilateral mastectomy, then I think you certainly should follow appropriate screening. That screening should include mammograms, but it might also need to include breast MRIs. So you should talk to your doctor about the need or possibility for breast MRIs.

Could you [make] . . . lifestyle [changes that will help fight the cancer, and] decrease th[e risk of recurrence]? I'll talk . . . about it. Lifestyle changes really haven't been proved to reduce the risk of breast cancer. Exercise might, but it's not been tested, although there's a clinical trial described here at this meeting . . . On the other hand, exercise, a healthy diet and avoiding alcohol are [generally good to do] . . . I do recommend that for everybody who's had DCIS breast cancer, . . . [although] . . . we don't have the degree of risk-reduction that would be expected from that.

So, to conclude, breast cancer [is] commonly diagnosed at the DCIS level. It can be detected with mammogram and MRI. Prevention of invasive disease is the goal. Size, grade, location, estrogen receptor [status] all affect treatment. Surgery, radiation, [and] tamoxifen are options to discuss. Clinical trials are available for ER negative and HER2 positive DCIS. Most importantly, after you've had that treated effectively, make sure you continue to have appropriate screening, because there is the significant risk of developing additional DCIS or invasive breast cancer.

So that's it. We can spend the rest of the time just asking questions. Go ahead.

WOMAN:

Have you found many cases [of DCIS]? I was diagnosed with . . . DCIS, but I had a lumpectomy, chemo, radiation. I guess they thought it was a clogged milk duct, because I was pregnant at the time. I heard you say most people don't get —

POWELL BROWN, MD, PhD:

Did they [find any] . . . invasive cancer at all?

WOMAN:

It wasn't — no invasive cancer. It was four centimeters. It was clear margins, whatever, they operated, you know, took [it] out.

POWELL BROWN, MD, PhD:

What chemotherapy did they give you? Do you remember?

WOMAN:

I had Adriamycin, Cytoxan . . .

POWELL BROWN, MD, PhD:

That would be very unusual for DCIS alone. It makes me suspect maybe they saw invasive cancer there. Did you have lymph nodes removed?

WOMAN:

No lymph. They [did scans to look for cancer elsewhere], but nothing showed up. I had nothing removed.

POWELL BROWN, MD, PhD:

That would be unusual in pure DCIS. That makes me think — I wonder if there wasn't some invasive component there.

WOMAN:

So it's now been four years later, and I'm still not showing any [signs of recurrence].

POWELL BROWN, MD, PhD:

Good. Excellent. Although I want to get back to your question that I sort of panned off before. The question you asked me before: soy . . . flaxseed. The use of soy, flaxseed and other phytoestrogens or plant estrogens, these are weak estrogens. There's nothing magic about them. They're just weak estrogenic compounds. The way I describe it: Soy has been reported to be cancer-preventive in some studies. Soy has been reported to maybe promote cancer in other studies. Soy is commonly used to treat hot flashes in postmenopausal women. Soy is used in premenopausal just because it's healthy. . . [Laughter]

So, soy, black cohosh, [Evening] Primrose [Oil], all those, they have some estrogenic activity. They do stimulate the estrogen receptor. If you're



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a premenopausal woman, you have a natural estrogen in you that's much more potent. The soy will not increase stimulation of the breast tissue more than the circulating estrogen you normally have, [but] it might interfere with that circulating estrogen. Therefore, in premenopausal women, there's at least a theor[y] ... that soy products might prevent cancer, because they might interfere with the natural estrogen that you have in your body, which is a strong estrogen. But in the postmenopausal setting, where you have very low estrogen levels, if you take soy, even a weak estrogen is higher than your natural estrogen in that setting. So in the postmenopausal setting, soy can actually stimulate the breast tissue and theoretically could promote cancer.

So I generally tell postmenopausal women not to take soy just to take it. In premenopausal, if they want to take soy I'm not so worried about it. But if you've had cancer premenopausally, I would [not] use soy to try to be your method of choice to block the estrogen receptor, because there are a lot better estrogen-receptor blockers, like tamoxifen or Faslodex or others. If you're postmenopausal, ... you're having hot flashes and ... you're telling me you're about to take estrogen because these hot flashes are so bad, I'll say, "Well, try soy." Because it's better than taking the estrogen, and it might work. So, it's complicated. ...

WOMAN:

I just had a question, because you talked a little bit about the difference between tamoxifen in premenopausal and postmenopausal women. But I was wondering: [Is] DCIS itself different [in premenopausal and postmenopausal] women? Does there tend to be a difference between what [kind of treatment] a younger woman gets and [what kind] an older woman gets ...?

POWEL BROWN, MD, PhD:

Potentially, yes. It's not much different than invasive breast cancer in this way. So this is an answer both for DCIS and invasive cancer. As you know, young women tend to get estrogen-receptor negative breast cancer. Older women typically get estrogen-receptor positive breast cancer. Said another way, in postmenopausal women, they get a better-prognosis breast cancer, usually. Younger women, under the age of 50, generally get a worse-prognosis breast cancer. That's true with DCIS. The high-grade DCIS is more common in young women than it would be in older women.

WOMAN:

What is your feeling on Zoladex ...?

POWEL BROWN, MD, PhD:

For treatment of cancer? ... We're not talking about DCIS anymore. All right? Zoladex is not used at all for DCIS, and I don't recommend it. Now, we just switched into another [line of thought] where they're talking about treatment of early-stage breast cancer in premenopausal women. We know aromatase inhibitors are useful in postmenopausal women. So there's a great interest in trying to use them in premenopausal women. But we have to make them postmenopausal, in a sense, to get that activity. ... To do that, [you can] either surgically ... remove the ovaries, or use Zoladex to ... chemically induce menopause. That can be ... a useful strategy. It's being studied in clinical trials, so I'll be more definitive when those trials come out. [Once they do, it could be] a potentially good way to treat premenopausal, ER positive breast cancer.

WOMAN:

How much vitamin A [should] ... [a] women take [if she has] ... DCIS or a history of it?

POWEL BROWN, MD, PhD:

That trial [I discussed earlier] did not say that everybody should take vitamin A. It's actually a vitamin A drug or derivative that is very effective at preventing cancer in animals, and it looks promising in women. But it's not to the level of making a recommendation. So, that's the long answer. The short answer is I'd just take a multivitamin.

WOMAN:

Okay. I had a couple of questions. One is about soy in conjunction with tamoxifen. Is there any —

POWEL BROWN, MD, PhD:

Oh, yeah. I should [address] that.

WOMAN:

Is there any relationship? Then also about ovarian suppression for DCIS, because that's what I'm doing. I've been taking Lupron for two-and-a-half years.

POWEL BROWN, MD, PhD:

... I'm very uncomfortable using soy products when you're taking tamoxifen. ... Both [tamoxifen and soy are] metabolized by the liver, and you can interfere with your metabolism of tamoxifen if you take soy. ... You can basically render tamoxifen

useless. So [if] you're taking soy, you can block the effects of the tamoxifen. So don't take tamoxifen and take soy unless your doctor has said to do that, and th[at regimen is being] regulat[ed] ... or monitor[ed]. ... In most cases, you don't want to take soy with tamoxifen.

WOMAN:

Is that [true of] black tea, too?

POWEL BROWN, MD, PhD:

Well, yeah. I don't really like ... [combining] ... tamoxifen ... [with] ... a lot of the other plant-based products. But some women have to. I would rather you do that than ... go off the tamoxifen or take estrogen. So it's a negotiation between your physician [and you]. But bring it up, okay?

Your other question is: Should you use ovarian-suppression to treat DCIS? ... The short answer is, "no." It's being tested in clinical trials but it's not standard-of-care. Now, theoretically there should be a benefit. I mean, just like in breast cancer treatment it looks beneficial. But it's not standard-of-care by any means. ...

WOMAN:

I just started taking tamoxifen in January. But back in '88, I had a blood clot in my right groin. So what are your thoughts on that?

POWEL BROWN, MD, PhD:

I don't like that.

WOMAN:

We took ... [more than] ... ten blood clotting-type tests and they came back showing that I had ... minimum risk for blood clots. ... We started on tamoxifen anyway.

POWEL BROWN, MD, PhD:

I don't like that.

WOMAN:

I don't like it either. [Laughter]

POWEL BROWN, MD, PhD:

And, in general, I don't [recommend] ... tamoxifen [to people who have] had blood clots.

WOMAN:

I mean, so long ago?

POWEL BROWN, MD, PhD:

Yes. So, I'd try to come up with other alternatives for you, if there are any. So you're taking [tamoxifen] for DCIS, for prevention or for invasive breast cancer?



WOMAN:

I had invasive —

POWEL BROWN, MD, PhD:

Are you pre- or post-menopausal?

WOMAN:

Well, you know when you go through chemo[therapy] you can very well [appear to] be menopausal.

POWEL BROWN, MD, PhD:

Right.

WOMAN:

So right now she's treating me as if — we won't know [whether I am pre- or post-menopausal] ... until a year out.

POWEL BROWN, MD, PhD:

So ask her —

WOMAN:

So right now I am post —

POWEL BROWN, MD, PhD:

Ask your doctor about this therapy that this person had over here, which was the ovarian-suppression with Zoladex and then an aromatase inhibitor, which is — I mean, again, I don't want to practice medicine for each of you, but that's what I'd do in you[r case]. [Laughter]

WOMAN:

I had a question about the tamoxifen, for metabolism of tamoxifen and what it means if ... you've had DCIS and you say, well, in my case, I'm an intermediate metabolizer. So I've been taking the tamoxifen.

POWEL BROWN, MD, PhD:

So, the CYP 2D6 Test for Tamoxifen Metabolism has wreaked havoc in our clinics now. We never use that test. ... I said you've got 50 percent reduction, [and that refers to] ... all-comers, without ... using CYP 2D6 to see if you're the good candidate. That said, it's looking like it might be a useful test to stratify people who take it. If you're an intermediate metabolizer, you're [likely to have the same benefit] ... as a normal metabolizer, and thus you should take the medication. ... If you're intermediate and high metabolizers, you should take tamoxifen. If you're a poor metabolizer of the tamoxifen ... maybe you won't get a benefit [from taking it] ...

We're ... on the verge this year of potentially using this information. There aren't really any great guidelines. But the answer is in [the] cancer, physicians are beginning to use this test to decide who would take tamoxifen. In DCIS, it's not been used for that purpose, but it's not unreasonable to [consider the results of CYP 2D6 testing]. ... In prevention settings, [CYP 2D6 status has] not been used [to determine treatment plans]. We're just looking into that now.

LANITA MOSS:

Well, thank you, Dr. Brown. [And, to the audience] ... make sure ... you fill out your evaluation form. ... We do read them, and we do [use] your feedback [to] plan [for] next year.

POWEL BROWN, MD, PhD:

Evaluate that highly, positively. [Laughter] Thank you very much. I've enjoyed it. [Applause] I look forward to the conference, too.

LANITA MOSS:

... Thank you very much. Have a fabulous, fabulous weekend. I hope you guys gain a lot from it.

[END OF TRANSCRIPT]