



## Understanding DCIS and LCIS

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### **ELYSE S. CAPLAN, MA:**

Good evening, everyone. My name is Elyse Caplan, and I'm the education director at Living Beyond Breast Cancer. It's very nice to see some familiar faces from past networking meetings, and it's very nice to see a lot of new faces. Tonight's topic, "Understanding DCIS and LCIS," is the first time we've offered this very specific topic since I've been at the organization, which is almost nine years. Clearly we're filling a need, because this topic is of high interest to people with a specific diagnosis that is very different from invasive breast cancer. You're here tonight, and you will hear much more about it.

Let me tell you about Dr. Paul Gilman. He is the chief of hematology/oncology, the medical director of the cancer program and the director of the Lankenau Breast Cancer Multidisciplinary Treatment Group at Lankenau Hospital [<http://www.mainlinehealth.org/oth/Page.asp?PageID=OTH000886>]. Dr. Gilman is an assistant professor of medicine at Jefferson Medical College [<http://www.jefferson.edu/main>], and he founded the oncology clinic at St. Joseph's Hospital in 1985. Dr. Gilman has received a National Cancer Institute grant and is a principal investigator for several regional oncology group trials. He has a much longer resume, but I'm going to keep it brief for now. Dr. Zonera Ali is a colleague of Dr. Gilman's, also a hematologist/oncologist at Lankenau Hospital, and she is the co-investigator with Dr. Gilman on many clinical trials for the prevention or treatment of breast cancer. Please welcome Dr. Gilman and Dr. Ali. (Applause)

### **PAUL B. GILMAN, MD:**

It's a pleasure to be here this evening and a pleasure to be working again with Elyse and LBBC. I'm going to start by apologizing for my voice. Since Elyse said I started that oncology clinic in 1985, when I tell you this is the first time I've had laryngitis in all my 30 years, you're not going to

believe the "30" part. But it really is the first time I've ever had laryngitis. I do apologize, and if you have any difficulty hearing me, hopefully the microphone will work.

I'm going to discuss DCIS, or ductal carcinoma in situ, and Dr. Ali will then discuss LCIS. Then both of us are going to have a discussion about high-risk individuals, particularly individuals with LCIS and atypical hyperplasia, and our approach to individuals like that. The first question really is: What is DCIS, ductal carcinoma in situ, noninvasive ductal carcinoma? Essentially it is a malignancy of the cells that line the milk duct of the breast. Yet the cells, despite having become malignant or cancerous, have not left their position in the milk duct. They remain in their position. They start to proliferate, as we call it, or grow, and they start to fill that milk duct with malignant cells, but they don't start to spread in the other direction into the surrounding breast tissue.

Imagine a tunnel through a mountain, and the bricks within that tunnel have become cancerous and start to multiply, and they start to fill up that tunnel, but none of them are growing out into the soil of the tunnel, or beyond the duct. It is intraductal cancer, noninvasive ductal carcinoma. Now, sometimes it can be difficult to distinguish, not typically from invasive ductal carcinoma, but there is an entity that we call atypical ductal hyperplasia, where the cells start to proliferate, to overgrow, and look very abnormal but are not yet malignant or cancerous, and our treatment approach is different.

In terms of how this type of cancer presents, many years ago, way back in 1985, we saw very little in the way of DCIS. It probably constituted less than 1 percent of the breast cancers that we see. Currently we feel that DCIS probably now makes up over 20 percent of the breast cancers that we see, and that number is continually increasing. Just a few years ago, it was estimated that probably in a single year, 60,000 women or

more would be diagnosed with DCIS. Why is that? What is the difference? Very simply, the difference is screening and mammography. Basically, early detection by mammograms is why we're seeing so much more DCIS.

DCIS is a very early form of breast cancer. When we talk about the stages of breast cancer, you know that we talk about stage I, stage II, stage III, stage IV. On that scale, DCIS would be considered stage 0. It is a malignancy; it is a cancer. But, in a way, the importance is that it may just be a precursor to invasive cancer, and that has to do with some of the issues in terms of how we treat DCIS. Typically it is found very early. Occasionally we see a patient with DCIS with a lump you can actually feel in the breast, but the vast majority of patients – probably about 90 percent to 95 percent of patients with DCIS – are detected by an abnormal mammogram. Maybe 5 percent to 10 percent have a lump that you can feel or a discharge from the nipple. It is really a diagnosis by mammogram.

What is it that we see on the mammogram? Typically, unlike invasive cancer, we don't see an abnormality that suggests a growth or a mass. What we see is a cluster of what we call calcifications, or microcalcifications – little flecks of calcium. There's calcium in the breast because the breast is a milk-producing organ. Calcium is a major component of milk, so there's calcium in the breast. We see little depositions of calcium within the breast, usually in a defined little cluster. Now, you can see various forms of calcifications. The radiologist who is the expert in mammography can look at a mammogram and say, well, these calcifications look benign, or these calcifications are very suspicious or look like they're very likely to be malignant.

What we're looking for are the little flecks of calcium in a cluster, and sometimes they can be what we call linear. They look like little tiny needles of calcium. Those we more often see with an



invasive cancer. If we see little granules of calcium that look like little pieces of salt, like you took kosher salt, the real thick granules, and sprinkled it in a little cluster, that's the typical appearance if we're going to see DCIS on a mammogram. When we see that little cluster of calcifications and it prompts a biopsy, in probably about two-thirds of patients what we're going to find – if we're going to find a cancer – is DCIS. In another one-third of the patients, we're going to find DCIS with just a little bit of microscopic invasive cancer. That really adds up to 100 percent, but it falls a little short, and in a small percentage of patients, we might actually find that it's an invasive cancer.

That little cluster of microcalcifications is concerning, but it's already telling us that it's highly likely that we are treating and facing a very early-stage, very favorable cancer. What is our next step? When we find this little cluster of calcifications, what do we do? If there's a lump that you can feel in the breast, if there's a mass that you can see by ultrasound, we could do fine needle aspiration, where you just put a needle in, aspirate some cells and see if there are malignant cells there. This situation doesn't really lend itself to that.

In the past, what would have to be done is what was called a needle-localized excisional biopsy. The radiologists would do a mammogram, and based on the mammogram, they would insert needles perpendicular to each other. They would intersect through that little spot where those calcifications were. The surgeon would then take the patient from mammography to the operating room and excise that area. That was the way you had to diagnose this, because there was nothing you could feel on your exam; there wasn't a mass that you could see on mammogram or ultrasound.

These days, that procedure is still sometimes done, but now what we very frequently do is what is called stereotactic biopsy. This is something that is done by the radiologist, typically the mammography specialist. It utilizes the technology of mammography but in a three-dimensional fashion, so that they can three-dimensionally line up where this is within the breast and insert needles, drawing out a little sliver of tissue – what is called a core biopsy – and thereby make the diagnosis.

When we have a core biopsy that shows DCIS, typically we're going to go on to treatment, which involves excision. But even were we not planning necessarily to excise this, or were we planning just to call this DCIS by virtue of core biopsy, it still is

important that we do an excision also, just to be sure that there isn't any associated component of invasive cancer along with the DCIS.

When you see a pathology report that comes back saying DCIS, intraductal carcinoma, there are a whole variety of terms that become important in terms of prognosis as well as our treatment recommendations. You'll see terms like comedo, papillary – these are terms that refer to what the appearance under the microscope is. How are these cells growing? How is it that they're filling up these milk ducts? Some have this solid appearance. Some have what we call a cribriform appearance. All of these appearances may relate to some degree to the prognosis. What we have found most helpful in the biopsy is looking at what we call the grade. When we look at invasive cancers, we're always talking about grade.

With DCIS, we're also talking about grade, particularly when we look at the nucleus of the cell. We talk about grade 1, 2, 3. Grade 1 basically looks almost benign. It doesn't look particularly aggressive. It doesn't look highly malignant. Grade 3 clearly looks very bizarre, very different from what the normal appearance should be, and is considered high grade or very aggressive. Grade 2 is basically anything that falls in between. It becomes important in our treatment planning to know whether we're dealing with grade 1, grade 2 or grade 3 DCIS.

There is also what we call necrosis. These tumors will often have little bits of dead tissue within them. As they grow, some of the cells die, and we'll see what we call necrosis, which is just dead cells or dead tissue. The presence of necrosis indicates to us that we're dealing with a more extensive DCIS. When we see that on the pathology report, that carries importance as well.

We look at these things perhaps on the core biopsy. We've made a diagnosis of DCIS. We look at the mammogram. What do we do next? What do we do as far as any other staging? What do we do as far as treatment? In terms of treatment of a DCIS, not too many years ago, the standard treatment was a simple mastectomy. The cure rate was very high. It was probably 96 percent, 97 percent. It was really at a point where women started asking the question, and then physicians started asking the question. We have decided that for a woman with a stage I or stage 2 invasive ductal cancer, you don't have to lose your breast. We can do a lumpectomy and treat with radiation. Here we're saying, you've got a

stage 0, much more favorable cancer, and yet we're simply saying it's a mastectomy.

There was a clinical trial that looked at the role of radiation. The trial then subsequently looked at lumpectomy, just removing the DCIS, versus lumpectomy followed by radiation to the breast. To some degree, a bit of controversy still remains, though for the most part radiation is an accepted part of treatment when we talk about breast conservation in patients with DCIS. One option for a woman diagnosed with a DCIS is to have a lumpectomy – remove the area where the cancer is, with some margin of normal tissue around it – and then subsequently treat the remaining breast with radiation.

In terms of successfully accomplishing the cure of the DCIS, the key is that we adequately remove the area of concern. Often times, a mammogram of the removed tissue will be done to see if it looks like it contains that cluster of calcium deposits. The other thing is a follow-up mammogram afterward to help assure that, indeed, the area of concern has been adequately removed. The other key is what I mentioned before about a margin of normal tissue around the cancer. That becomes very important in terms of successful outcome in breast conservation with or without radiation. It becomes very important that there is no DCIS within the margin. If there is, it would typically mean what we call a re-excision: go back, remove some more tissue, with the attempt to try to remove all of this with a negative margin – normal tissue without cancer in it – to then be able to proceed with radiation to the breast.

There were some studies done, some that we were part of, that looked at the idea of if we have a very favorable DCIS – the DCIS is low grade, maybe at most grade 2, so it's not real aggressive looking – and the surgeon removes it with a good margin of normal tissue around it, can we avoid radiation in this instance? To date, there appears to be a small group of patients with very favorable DCIS who may, indeed, do well without radiation. But for the majority of patients, when we look at the risk of recurrence in the breast – and recurrence could mean another DCIS or might this time mean an invasive cancer – the results clearly appear to be better with radiation treatment as opposed to lumpectomy alone.

The other treatment that is still used is mastectomy. There are indications for mastectomy, one being if a woman's preference is to have this treated with mastectomy. It is certainly a reasonable



and very successful approach to treatment. The other time is if the surgeon is unable, with multiple attempts, to achieve negative margins – the surgeon keeps trying with re-excisions, which are not successful. Finally, if it is truly what we call a multifocal cancer – that is, if there are multiple little areas within the same quadrant of the breast that might be able to be removed, and then treatment with radiation carried out. But if there is clearly evidence of scattered cancer or deposits of calcium well throughout the breast, that's a situation where we know that the recurrence risk is going to be excessively high, and we know that mastectomy would be the best option.

The surgeon proceeds, either with a lumpectomy or a mastectomy. Knowing about invasive cancer, part of that typically is to evaluate the lymph nodes under the arm, the axilla. For most women these days, that means a sentinel lymph node biopsy. Do we do that with DCIS? The answer for the most part is no. DCIS, or noninvasive cancer, has a very, very low likelihood of spreading, an extremely low likelihood of spreading to the lymph nodes and, as a result, an even lower likelihood of spreading anywhere beyond the lymph nodes. So, typically, in a woman undergoing lumpectomy, that would be the only surgery. There would be no role for a lymph node biopsy.

If a woman has a biopsy that shows a little bit of invasive cancer – what we call microinvasion – then even that little bit justifies doing a sentinel node biopsy. If a woman is going to be treated with mastectomy, then in that instance we do a sentinel node biopsy. The question is: Why would we do that? If we do the lumpectomy and the pathologist comes back and says, "I found a little bit of invasive cancer in that specimen," the surgeon now needs to do a sentinel lymph node biopsy. They can go back and do the sentinel node biopsy, injecting the dye or the radioactive material into the site where they did the lumpectomy and tracing it out to the lymph nodes.

If the surgery was a mastectomy and the pathologist comes back and says, "Either in that tumor or elsewhere in the breast, we found some invasive cancer," the surgeon needs to do a lymph node biopsy. But because of the way a mastectomy is done, the lymph vessels – those channels – have been disrupted. There is not an effective way of doing a sentinel lymph node biopsy, so the surgeon would have to do the more traditional, more extensive lymph node dissection. So if the

procedure is a mastectomy, even if we're sure it's DCIS on the biopsy, typically a sentinel node biopsy would be done.

Now, we've talked about what I would term local therapies: surgery, radiation. Is there any role for systemic therapy? There is. This is an area that really requires very much a thoughtful team effort between the treating physician and the patient – really sitting down and weighing the pros and cons, the risks and benefits of treatment. Up until 1999, it was felt that treatment was either surgery – a mastectomy – or lumpectomy and radiation. There was no role for any systemic therapy. In DCIS, there is clearly no role for chemotherapy. That's a given. There is never a role.

However, in 1999, the results of a study came out that showed that women who were treated with tamoxifen following lumpectomy and radiation might have a better outcome. They might have fewer recurrences of invasive or noninvasive cancer in that breast, and they had fewer invasive and noninvasive cancers in the opposite breast. Now, the differences weren't overwhelming. The percentage of women who had something happen to their breast – a new cancer in the other breast, a recurrent cancer in the treated breast – roughly, without tamoxifen, is a little over 13 percent; with tamoxifen, a little over 8 percent. It's a very statistically significant difference, but is that clinically significant? Is it significant for an individual woman?

This is where the discussion has to be held about the side effects of tamoxifen, the risks associated with it, the benefits, the outcome if tamoxifen is not given. Basically, there is a role for tamoxifen. At this moment in this country, probably at most about half of women diagnosed with DCIS end up taking tamoxifen. Some of that is because of some reluctance on the part of treating physicians because of side effects versus benefit; some of that is because of the reluctance of women themselves when they weigh the benefits versus the potential side effects.

What is the outcome? What is the prognosis? The key thing to focus on here is that DCIS is a very early form of breast cancer that carries a superb prognosis. It does carry a small risk, with adequate treatment, of recurrence or the development of an invasive cancer, but basically the treatments we've talked about – surgery, radiation, tamoxifen – all impact the effect in the breast, either the treated breast or the opposite breast. None of these really have been shown to

have an impact substantially or significantly on a woman's survival. Does that mean our treatments are not successful? Not at all. It's just that the survival statistics are so good with DCIS that these treatments really don't have any room for improvement. We're dealing with a very, very favorable cancer.

The key after the diagnosis and the treatment then becomes regular surveillance, and routine breast examination and, very importantly, routine mammography are important. This is one area where perhaps MRI is not all that helpful. The mammogram can pick up some small DCIS that the MRI will actually miss. But careful follow-up with mammography for recurrence or a new cancer in the other breast becomes particularly important.

One last note: In terms of anything investigational, there is some interest right now because of the fact that many DCIS tumors are what we call HER2 positive, and many of you know about Herceptin and invasive breast cancer. There is some interest now in looking at the use of Herceptin in DCIS. It's something we have to look at carefully, because now we're moving toward drugs that are more expensive, less cost-effective and potentially more toxic in a type of cancer that already starts out with a superb prognosis. With that, I'd like to stop and turn the microphone over to Dr. Ali.

#### ZONERA A. ALI, MD:

Thank you. DCIS, as Dr. Gilman said, is a precursor for breast cancer. LCIS is not a precursor, but when somebody has LCIS, we know that those people are at a high risk of developing an invasive breast cancer. [With] DCIS, if you have a lesion, you want to remove it. If you see something on the mammogram, you want to remove it. You know that by removing it, the chances of this person ever developing invasive breast cancer become much lower. On the other hand, LCIS is normally not seen on mammogram. Somebody would have felt something, or had a biopsy for something unrelated and found some cells that look abnormal, but those cells themselves do not become malignant.

That's the main difference, I would say, between DCIS and LCIS. The problem with LCIS is if you have been diagnosed with LCIS, you are at a high risk of developing invasive breast cancer down the line.

What is that risk? That risk is almost 1 percent each year. Say somebody is diagnosed at the age



of 39. Normally, the LCIS is driven by estrogen. Our estrogen normally peaks when we are premenopausal, so a lot of people who get diagnosed with LCIS tend to be premenopausal females in their 40s or late 30s. When somebody has been diagnosed with LCIS, with each year, their chances of developing invasive cancer become higher. It's almost 1 percent each year. If somebody was diagnosed, say, at 40, at 60 that risk could be 20 percent, which is fairly high risk.

Unlike DCIS, the more important thing with LCIS is to have good surveillance. Because the cancer itself, the cells themselves, are not going to become malignant, taking that breast out is not going to help. Actually, they looked at, if somebody has LCIS, what are the chances of developing breast cancer in the opposite breast? Interestingly, they found that in the opposite breast, there was a high risk of developing invasive cancer. So, if somebody has LCIS diagnosed today, and if we were to follow her down many years, there is high likelihood – with that study, there was a 54 percent chance of developing invasive breast cancer in the opposite breast and a 46 percent chance of developing it in the breast where the original biopsy was done.

The first thought you always have is, “I have cancer. Take it out.” But taking it out is not going to do anything, because it's more likely that it's going to happen in the opposite breast. In that sense, it sometimes becomes even more difficult to follow such people. What is the right decision? Do we do bilateral mastectomies? That's a harsh, big surgery where, yes, there's a potential of this person having a malignancy. But we can follow such patients. Often, the surveillance is the most important thing. What does surveillance mean? Surveillance often means that we are following such people with breast exams, normally every six months, mammograms.

Even though the LCIS itself is not picked up by mammogram, the reason we are doing mammograms in such people is because we want to pick up that invasive cancer at a much earlier stage. That's the reason for breast exam, too. You basically are doing an examination looking for lymph nodes, the breast itself, so that if there is something you are able to pick it up early. MRI's role is controversial, but MRIs are something we are definitely looking at for high-risk people, because MRIs are more sensitive in picking up something that is smaller. The only problem with MRIs is that they often pick up things that are

not invasive, too, so often people undergo biopsies that might not have been really needed.

The other thing Dr. Gilman talked about with the DCIS is that there is also the option of just doing medications, such as tamoxifen, or something called raloxifene, or Evista. One of the large studies that came out maybe a year, a year and a half ago, showed that people who have LCIS – or, for that matter, DCIS – if they took tamoxifen or raloxifene, and we followed these people over many years, their risk of developing invasive cancer was lowered by taking this medication. When you look at overall survival – how long somebody lived – it didn't make any difference, but when you looked at the incidence of invasive cancers, it was definitely lessened by taking tamoxifen and raloxifene.

If somebody had a biopsy and it turned out to be LCIS, how do you follow it? One of the things you want to make sure of is that you have done more biopsies, because it is a marker for invasive breast cancer. You want to do more biopsies to make sure that there are no invasive cancers in there, because if there are invasive cancers, then you need to deal with that invasive cancer itself. That's where it becomes a little bit tricky as compared with DCIS.

If you have a family history of cancer, there is a high risk of developing LCIS in such people. What is the overall risk of developing LCIS? Unlike DCIS, which we know has been increasing – more so because I think we have become much better at mammogram – they looked at the autopsy reports, and it is very, very uncommon. They found it in less than 1 percent of the population. It's not as common as DCIS, but at the same time, we do see cases. I saw at least, I think, five, six hands go up here. Among us sitting here are people who have been diagnosed with LCIS. Often, how to follow such people or how to do the surveillance or whether to take tamoxifen or raloxifene is a discussion that you have with your surgeon or a medical oncologist, depending on which place you are at. Dr. Gilman, do you want to come and talk about high risk?

#### **PAUL B. GILMAN, MD:**

Both of us want to address the issue of women at high risk. In particular we're talking about, with this evening's topic, LCIS, which itself is a risk factor, as Dr. Ali has outlined, and, as I mentioned briefly, what we call atypical hyperplasia, where there's the overgrowth of cells. It can be lobular or

ductal. They look abnormal but not truly malignant. That is clearly one group of high-risk women. There are other things we look at, family history being one of the most important, and the degree of the relative – first-degree relative, let's say, versus a third cousin – and the age of the individual in the family: the mother having breast cancer at 46 versus a grandmother with breast cancer at age 80. These things have different impacts on the risk of breast cancer.

We know that we're able to identify high risk, and we can identify genetic high risk with BRCA1 and BRCA2 testing, which tells us about those individuals who might be at exceedingly high risk. If, after going through this whole process, we've defined that women are at high risk – let's say a woman has LCIS – what are our options at this point? One is surveillance. Just as Dr. Ali has already discussed, one option is just careful follow-up, routine examinations, breast self-examination, mammography and, in certain instances, MRI scanning as well.

If we have a woman who has a BRCA mutation – an abnormality in one of the so-called breast cancer genes, BRCA1 or 2 – or if we have a woman who has a first-degree relative – a mother or a sister, or potentially even a father or a brother – who has a gene mutation, and that woman has never been tested, that woman certainly could be followed appropriately by MRI scanning in addition to mammography. Also, if, when we put all of the risk factors together, we feel that a woman's lifetime risk of breast cancer is at least 20 percent to 25 percent, there is clearly evidence that MRI scanning is of benefit and certainly justified as part of the routine, careful surveillance on an annual basis.

There are other instances in which we do use MRI. As Dr. Ali has mentioned, we're not looking for LCIS. We're looking for the consequence of it, which is either a DCIS, which is probably picked up on mammography, or an invasive cancer, which may be detected by mammography or by MRI scanning. The other thing is that if a woman has certain other rare genetic disorders which predispose to breast cancer, there may be a role for MRI. Certainly, careful surveillance is an option here.

The other option would be to move toward treatment. If we say, well, this is a woman who's at high risk, is not necessarily entirely comfortable with just a passive approach, in a sense – and I wouldn't truly call it “passive” if you just opt for



surveillance, because it's a very active program of self-examination, physician examination, mammography, perhaps MRI, so it is really an active program. But if a woman decided that she wanted to do something more active and says, "I'd like to somehow treat the risk. What do I do to reduce my risk? Are there options? Rather than just simply recognize that I'm at high risk and monitor closely, what can I do?"

There are other options, both surgical and medical. I'll ask Dr. Ali to touch on those.

#### **ZONERA A. ALI, MD:**

As I said before, the option at that time often is bilateral mastectomy: Both of the breasts can be removed. Nowadays, it's unbelievable how good our reconstruction surgeons are. Often for our young patients, especially those who are BRCA1 or BRCA2 carriers who have a very strong family history, we would recommend it. Truthfully, it's hard to tell whether they have had a reconstruction. With BRCA1 and BRCA2, the other thing we would often talk about is also having their ovaries out, because those people are at a high risk of ovarian cancer.

Other than the surgical issues, can we give them treatments, as I said before: tamoxifen or raloxifene, which is Evista, often used in females for osteoporosis. Both of them have shown in a trial – it's called the STAR trial [<http://www.cancer.gov/STAR>], which came out around one-and-a-half years ago – that in people who were at a high risk, both of them decreased the chances of developing invasive cancers.

As you can see, there are many, many options here: surveillance, surgery, surveillance with medical treatment such as tamoxifen or raloxifene. If somebody has bilateral mastectomy, then normally they would not require tamoxifen, because the reason you are using tamoxifen or raloxifene is because you want to decrease the chances of developing invasive breast cancer. If somebody already has had both of her breasts removed, it's not any benefit because she doesn't have any breast tissue left in there. Those people, therefore, do not require any type of chemical treatments with medications.

#### **PAUL B. GILMAN, MD:**

Before we open it up to questions, just a couple of other thoughts. One, for a woman who opts to have prophylactic mastectomy, I think it's very, very important for that woman and her physician or surgeon to realize that that is a highly effective

procedure, that it reduces the risk of developing breast cancer by 90 percent to 95 percent. Only one study suggested that perhaps it was 100 percent, so I think it's important to realize that there is still a very small risk. The feeling is that there probably are little nests or nests of breast tissue within the chest wall that conceivably could become cancer – a very small chance of that. Again, a 90 percent to 95 percent risk reduction. But we always urge women who have had prophylactic mastectomy to still continue follow-up programs, not necessarily mammography or MRI, but certainly routine examinations with their physician on at least a twice-a-year basis as well as self-examination.

In terms of medical therapy, we talked about tamoxifen. We've talked about raloxifene. I think Dr. Ali is a lot younger than I am, so she was probably still in medical school when we were doing the PI study [<http://jnci.oxfordjournals.org/cgi/content/abstract/90/18/1371>] that I was involved in, which was tamoxifen versus placebo in high-risk women. A couple of important things came out of that. One is for a woman to be in that study, she had to have gone through an assessment of what her breast cancer risk was. There were a number of things that were looked at: family history, number of biopsies that she might have had in her lifetime, atypical hyperplasia on a biopsy. There was a score assigned to this through a formula.

If the woman was felt to have a 66 percent increased risk of breast cancer – that was the number that was determined – she was considered high risk and could go on the study. However, if a woman was 60 or older, she could simply go on the study without any need to worry about any other risk factors or formulas. So, it does point out that the two most important risk factors with breast cancer for the general population are, number one, being a woman; secondly, as women grow older, the risk goes up with age. I think that's important to keep in mind also.

The other thing is the use of tamoxifen. I discussed it in regards to DCIS. One of the classes of drugs that we haven't discussed this evening is the aromatase inhibitors, drugs like Arimidex, Femara, Aromasin. The reason we haven't discussed them is these drugs have been studied versus tamoxifen in all stages of breast cancer – metastatic, early-stage invasive cancer – and have been shown to be probably more effective and somewhat safer.

They have been studied in DCIS, but the trial results still are not available. The one major trial that we were part of closed to entry of new patients about two years ago, and we're waiting for the data to come out. So, the standard in DCIS still remains tamoxifen.

The aromatase inhibitors have not been looked at in high-risk women. There was a tremendous controversy, probably about a year ago, because tamoxifen had been studied versus placebo in the study with 19,000 women. Then, in a larger study with probably around 24,000 women, as Dr. Ali has said, it was studied versus raloxifene, or Evista. Both of those drugs came out about even. They showed the same reduction. They cut the incidence of breast cancer by about half in high-risk women. It was felt that raloxifene might be a little better because of a little more favorable side effect profile, but the next step was to look at the so-called winner of that study – which, because of the more favorable side effects, was raloxifene, or Evista – and letrozole, or Femara.

A huge study was planned to look at that in postmenopausal, high-risk women. It was basically determined by the NCI that it didn't feel it was a necessary study or a useful study. There was tremendous controversy about that. The NCI director felt that its funds could be put to better use in that trial, so it's not clear whether that study will ever be done. We're not sure about the role of aromatase inhibitors in high-risk women who have never had breast cancer. We're still not sure, awaiting the data, about women with DCIS. Those drugs remain important in postmenopausal women with either early-stage invasive breast cancer or metastatic breast cancer. With that, I think we can pause here and open the floor to questions.

#### **ELYSE S. CAPLAN, MA:**

I want to thank both of you. It was a great tag-team approach. Well done. Thank you. I know I learned a lot; I hope all of you learned a lot. (Applause) I'm so glad you covered the aromatase inhibitors, because I thought, "I'm going to kick off the Q&A with a question about aromatase inhibitors," because at Living Beyond Breast Cancer, that is one of the questions that we hear from women with this diagnosis, because they are hearing about women with invasive breast cancer using aromatase inhibitors. It's been much more in the media, and the things that we hear about on the news are things that we wonder may apply to our situation. So, I'm really glad that you covered



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that. Do you have any idea of when that trial might have data reported? Is it three more years, or ... ?

**PAUL B. GILMAN, MD:**

I think it's probably going to be a few more years. I think the reason has to do with the fact that it was a trial comparing tamoxifen to anastrozole, or Arimidex [Editor's Note: This trial is called NSABP B-35; <http://www.cancer.gov/clinicaltrials/NSABP-B-35>]. It's what we call a double-blinded study. There was no placebo. Half of the women were treated with tamoxifen and half with Arimidex. Neither the women nor the treating physician knew which it was; the pill looked the same. The reason I think it's going to be a few years has to do with the very favorable prognosis of DCIS. To analyze a study like this, a certain number of events have to occur before you can do a statistical analysis. By events, we mean either a recurrent DCIS or invasive cancer in the treated breast, or a new cancer, invasive or noninvasive, in the opposite breast. Given the prognosis and given the fact that the prognosis might be even better still with women on treatment, and both groups are getting treatment, it could be a few years at least before enough events have occurred so the statisticians can really start to analyze the data.

**ELYSE S. CAPLAN, MA:**

Thanks for answering that. I'm going to get the microphone, and I'm going to try to switch back and forth. I'm going to start right here.

**WOMAN:**

Dr. Gilman, I've been diagnosed with DCIS. I'm 76 years old. The first recommendation that I received from my surgeon after he did two lumpectomies – he went in twice and still was not able to get clear margins – was to do a mastectomy, which I totally do not want to do. My medical oncologist has told me to take Arimidex, so now I'm really confused.

**PAUL B. GILMAN, MD:**

First, I would start by saying you look much younger than 76 – I have to tell you that. Secondly, I think that, as we talked about, one of the important things that has shown up in a number of studies – whether a woman undergoes lumpectomy alone, which more often than not we don't advise, or lumpectomy and radiation – is establishing a negative margin. It's probably just 2 or 3 millimeters of clear tissue around the cancer.

The reason is if there is not a negative margin, it suggests that the cancer is more extensive throughout the breast than we would think, and the recurrence rate is higher. It doesn't mean that you're going to have a recurrence. It just means that the risk is higher. If we say a woman who undergoes lumpectomy and radiation in some studies may have, at most, perhaps a 10 percent risk of recurrence, that number may be doubled or tripled at least if the margins are not clear.

So usually, in both invasive and noninvasive cancer, if the surgeon is unable to get a negative margin, the surgeon will often then say, "Well, this is a more extensive cancer. Because of the risk of recurrence, you would be better served with having a mastectomy." The other reason is that at some point the question is when to stop doing re-excisions, because one of the key aspects of this is the cosmetic outcome. Certainly, if a woman conserves her breast, it's not only reasonable, but, in my mind, it's essential that you have a favorable cosmetic outcome. If you have multiple re-excisions, you might get to a point where enough breast tissue has been removed that, when you add the effects of the radiation, the cosmetic outcome may be very unfavorable, and some women may ultimately be better served with a mastectomy followed by reconstruction.

Some of it depends on how much re-excision was done. Is there room to do some more? A woman may say, "Yeah, I understand the risk. I know that there's a higher risk of recurrence, and it may be an invasive cancer, but I really just want to go with the radiation." The radiation oncologist may be willing to do that with, again, a very clear understanding that, being unable to get a negative margin, the recurrence risk is higher. At the least, you may have to go through this whole business again with a DCIS, or, more concerning, you may have to go through issues of an invasive cancer.

**WOMAN:**

Are you saying that if I do the radiation without the clear margins, it won't be as effective?

**PAUL B. GILMAN, MD:**

Correct. The recurrence risk is clearly higher.

**WOMAN:**

Is higher.

**PAUL B. GILMAN, MD:**

If you take a woman who has lumpectomy with a clear, negative margin and then radiation, versus a woman who has a lumpectomy who does

not have a negative margin – there's still cancer in the margin – and then has radiation, that woman – the one with the positive margins, as we call them, involved margins – clearly has a significantly higher risk of recurrence of her cancer in the breast than a woman who had negative margins with her excision followed by radiation.

**WOMAN:**

I had a second opinion, and that surgeon suggested they would go in for the third time.

**PAUL B. GILMAN, MD:**

It's really a surgical decision. This is one I always defer to our surgeons, because I say to them, "You tell me. What can you do surgically?" If they feel that there's enough breast and enough remaining breast tissue that they can try to take a little more, and the outcome cosmetically, the appearance, will be favorable, then it's not unreasonable to try it again, with the understanding that it may or may not be successful.

Just to briefly touch on the second question, about the Arimidex: The standard therapy, based on the clinical trials that have been done, for DCIS would be considered to be tamoxifen. Is that an absolute? No. I've treated a few women with Arimidex or Femara because of inability to tolerate the tamoxifen, or sometimes complications of the tamoxifen. I've had women who sometimes have had recurrent vaginal bleeding, uterine polyps. We start to worry more about the uterine cancer risk. We have used the aromatase inhibitors in that instance.

Again, you have to weigh the side effects and risks of the aromatase inhibitor versus how much benefit you are likely to get. ... It's not unreasonable to use those, though the standard would be considered to be tamoxifen.

**ELYSE S. CAPLAN, MA:**

I think the take-home message is that everybody's breast disease is uniquely your own, so you really need to formulate your list of questions to take back to your doctors. Sometimes it is a second opinion or a third opinion that one needs in order to make the decisions that are really important to one's life, so keep asking questions.

**WOMAN:**

My question is regarding medical intervention. It was my understanding that the drug intervention is only for people who are ER/PR positive and not for people who are negative. Is that correct?



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**ZONERA A. ALI, MD:**

Yeah, that's a very good point. For LCIS, 100 percent of LCIS – LCIS would not happen if there was no estrogen. For LCIS, we normally do not do receptor analysis. For DCIS, we have now learned that the DCIS that will more likely to respond are the DCIS that have estrogen receptors on them. They basically can stain the tissue that is taken out in the core biopsy to see if there are estrogen receptors there, because tamoxifen basically is a medication that blocks the estrogen response on the tissue, on the cells. Our practice at Lankenau is that we would offer people who have estrogen receptor-positive cancer only the tamoxifen or raloxifene.

**ELYSE S. CAPLAN, MA:**

I want to piggyback on that. Is that for grade I as well as grade 2 or 3 – high grade versus low grade?

**ZONERA A. ALI, MD:**

It is for all of them, but the question really becomes, do you even offer tamoxifen for somebody with grade I? That, as Dr. Gilman alluded to, is something you need to sit down and talk to the physicians about, because those are often very benign, and how much is tamoxifen or that type of intervention going to make a difference? The benefits are very, very low for those people.

**ELYSE S. CAPLAN, MA:**

Thank you.

**WOMAN:**

This question is related to the same topic. I've come to understand that there is no treatment for ER/PR negative high grade, no medical intervention, if you had a bilateral mastectomy.

**ZONERA A. ALI, MD:**

Actually, even if it was an estrogen receptor-positive DCIS and somebody had bilateral mastectomy ...

**WOMAN:**

No, negative.

**ZONERA A. ALI, MD:**

For negative, yes. But what I'm saying is, even if it was a positive one, for bilateral mastectomy, we would not offer medical treatment, because the idea behind these drugs is to decrease the chances of invasive cancers.

**WOMAN:**

We don't hear too much about drug treatment or any other kind of treatment for the ER/PR negative people.

**ZONERA A. ALI, MD:**

Most probably this Herceptin trial will be interesting to see, but I'm sure that's why they are looking at trials that involve Herceptin, because some of those are HER2 positive cancers. I think going forward, more and more clinical trials are going to look at it. You are right about it. Because these are less than one-third of the cancers, that's why you don't hear so much about them.

**PAUL B. GILMAN, MD:**

One thing also with DCIS: Because the prognosis is so favorable in DCIS, it's different from invasive cancer. When we see a woman with early-stage invasive cancer, we take a different approach if the tumor is hormone-receptor negative, ER/PR negative, versus positive, because we know that's of prognostic importance. The risk of recurrence is higher if the tumor is hormone receptor negative. With DCIS, given the prognosis of DCIS, no real difference has been demonstrated. What's been demonstrated is that there is just not the value of using hormonal therapy like tamoxifen. For a woman who has an estrogen/progesterone receptor-negative DCIS, we wouldn't use tamoxifen. But we would do that keeping in mind that we're still dealing with something with an excellent prognosis and a particularly excellent long-term survival outlook.

**WOMAN:**

Thank you.

**WOMAN:**

My question has to do with, I suppose it's a little to the side, but pain following bilateral mastectomy. I'm going a little crazy because before the bilateral mastectomy, about 14 months ago, I was thinking that after the bilateral mastectomy, the pain will go away. It never occurred to me that there would be a condition wherein following bilateral mastectomy I have the same – for me, I identify it as cancer pain. Along with that, the margins were – I don't think they were not negative, but I was told by the doctor that I should always let everyone know that the margin was, I think, a 1/6th instead of an eighth of an inch. This was ductal carcinoma. It was independent in both breasts simultaneously. I had had every mammo for 14 years, but the mass in the left breast was

like 8 centimeters when it was ultimately detected not by mammo, not by ultra, but at the end of that same week by whatever you call it. What direction to go in? Because I can't ...

**WOMAN:**

[Inaudible] pain management like [inaudible].

**WOMAN:**

Yeah. I just can't believe that it isn't somehow invaded or infiltrated or whatever the word is. All of the conversation is about the great positive outcome. Yet I guess I'm wondering about what's going on with the few people who aren't in the positive outcome and why not and what to do.

**ZONERA A. ALI, MD:**

It is rare to see, but yes, people who have had mastectomy – as Dr. Gilman said, the important point is that mastectomy decreases the chances of developing cancer by 90 percent to 95 percent. But in 5 percent of people, it can recur. What you're alluding to more seems like scar pain, which can happen when somebody has that surgery. Even for lumpectomy, which I'm sure many people here have had, you do get some scarring pain. I wonder if the pain that you're feeling might be from scarring and the healing process of having had two major surgeries. I'm not sure whether you had reconstruction afterward, but ... there can be a lot of scarring associated with all of that. In spite of that, if there is somebody who has had bilateral mastectomies or even a single mastectomy, we do follow them regularly, because we worry about cancer developing in the skin.

Every Tuesday, we have this multidisciplinary breast conference where we discuss our newly diagnosed breast cancer patients. One of the patients is somebody who had a mastectomy and then felt something in the skin. We did an MRI in such patient, and definitely on MRI it looked like an invasive cancer. Then she had a biopsy, and that's what it proved to be. But I think what you're alluding to, because of the fact that it has remained there now for 18 months since the time of surgery, it sounds more like scar tissue. Often it does require discussion with your surgeon. Sometimes you have to see pain management people for such pain control.

**WOMAN:**

I have two questions. The first is, do the aromatase inhibitors have the same side effects as tamoxifen, in my case with yeast infections?



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The other question is, if your siblings who had breast cancer were your half-sisters, are you still at high risk?

### ZONERA A. ALI, MD:

Yes, even though it is your half-sister, you get – each of us has two genes. One we get from our mom, one from our dad. It's possible that you could have gotten the genes from the family which is half family. Therefore, yes, even though it is the half-sister, it is still important, because that would be considered a positive family history.

The other question was about the side effects of aromatase inhibitors versus tamoxifen. The common side effect often for both of them is hot flashes. That, I can tell you, for most people is about the same: 10 percent of people will have it bad enough; most of them tolerate it very well.

One of the side effects that is very unique to tamoxifen is that in the uterus it works as an estrogen receptor stimulant. It actually makes the uterine wall become thicker. That's why there is this slightly high risk of developing cancer of the uterus from tamoxifen, which is unique to tamoxifen and is not seen in aromatase inhibitors. It is a very rare side effect, but that's why, when we do put people on tamoxifen, we tell them that any type of bleeding that is unusual that is happening between periods, we need to hear about it, because that's how it would manifest. Both people on tamoxifen and those on aromatase inhibitors will talk about a discharge. Yeast infections are not common with both of them. They're really less likely to happen.

### WOMAN:

Hi. I was diagnosed with DCIS premenopausally, had a lumpectomy and radiation. My question is for you, because I was diagnosed premenopausal and I was put on tamoxifen. I did experience the unfortunate side effects of tamoxifen and had to have a total hysterectomy. Normally, the period of time on tamoxifen is five years. Because now I'm postmenopausal, is there a need for me to continue on a different – like, switch over to a different therapy after the five years is up? Or once I take the tamoxifen for five years, I'm done?

### PAUL B. GILMAN, MD:

For DCIS, it seems clear at this point – until any new data comes out – that the drug we typically use is tamoxifen, and we use it for five years. At the moment, there is no role for any treatment beyond the five years. If you are on

tamoxifen, you've now had the hysterectomy, and assuming your ovaries were removed and you're postmenopausal, the drug we would still recommend is tamoxifen. It becomes a safer treatment now because you've had a hysterectomy, so you've clearly eliminated the uterine cancer risk. The plan would be – because it was given to protect the breast, and that reason is still there – to finish five years of tamoxifen. Unlike invasive cancer, where we may treat beyond that for a postmenopausal woman, especially with an aromatase inhibitor, it's five years of tamoxifen and then stop.

### WOMAN:

I have DCIS, MRI diagnosed, so I feel very lucky. My mammogram was clear. I had a lumpectomy followed by radiation. At the time, I looked at MammoSite but did not enter the trial because you had to make decisions very quickly. Now I understand that even shorter radiation times have been evaluated and seem promising. What is the present status of radiation following lumpectomy for DCIS?

### PAUL B. GILMAN, MD:

Currently, the standard would be whole-breast radiation, which is the standard course of radiation therapy. Both in invasive and noninvasive cancer, there is a lot of interest in looking at partial-breast radiation. A couple of ongoing trials are looking at it. One is what we call a registry trial, where women who are treated with partial-breast radiation are simply entered into a registry to then be followed. That has been going on for some time. [<http://www.breastsurgeons.org/MammoSitePatientRegistry.htm>]

Then, for a little bit less time, there's a clinical trial through the NSABP [National Surgical Adjuvant Breast and Bowel Project], which has been at the forefront of a lot of early-stage breast cancer treatment since the 1970s. That trial, called B-39, is looking at partial-breast radiation versus whole-breast radiation in early-stage breast cancer [[http://www.nsabp.pitt.edu/B39\\_Information.asp](http://www.nsabp.pitt.edu/B39_Information.asp)]. Strictly speaking, it's investigational – we're still looking at it – but clearly, a lot of women are being treated with partial-breast radiation outside of a clinical trial.

There are different ways of doing it. One way is to insert catheters into the breast with radioactive material within them. Another way is to treat with MammoSite, which involves putting a balloon device into the cavity that's left after the

lumpectomy, and then, twice a day, putting a little radioactive seed in there. It's two treatments a day for five days and completed. A third way is to use external beam radiation, like what would be used for the whole breast, but with technology that allows the beam to be focused on just the area of concern. Most of the recurrences that are seen, particularly in DCIS, tend to be in the same area as the original cancer. That's the concept that perhaps we can just treat that area. Also, the concept is that if a cancer occurs in another part of the breast, there is still the option of lumpectomy and radiation. After lumpectomy and whole-breast radiation, if there is a recurrent cancer, most often that's going to mean a mastectomy.

Partial-breast radiation is being looked at. It's being used. It certainly appears to be an option, but, again, I think it has to be weighed carefully, and some of the factors that go into weighing it look at recurrence risk to begin with – so, they look at the size of the tumor, the size of the DCIS, the grade, how much of a margin there was, and the age of the patient also.

### ELYSE S. CAPLAN, MA:

We have a lot of questions tonight. I'm really glad that we have a lot of time for Q&A.

### WOMAN:

Left untreated, does DCIS always develop into an invasive breast cancer?

### ZONERA A. ALI, MD:

Not always, but we know that if we follow such people, most of them will develop invasive cancer. They looked at the chances of developing invasive cancer, and over years, it can be as high as 30 percent to 40 percent that invasive breast cancer will develop, which is a high risk.

### WOMAN:

I was diagnosed with DCIS about four years ago, but the initial doctor advised me that because the pathology results said it was well [circumscribed], solid, and the size was 0.5 cm, that I will not need radiation, but they will put me on Arimidex. But the pathology results also indicated that it was microinvasive, so I did not understand that. I told my surgeon that I would like a second opinion, so I went to Johns Hopkins to see medical oncology regarding the Arimidex, because already I agreed with the oncology radiologist that I will not take radiation.

When I got to Johns Hopkins, the doctor told me that I should take Arimidex, so I agree with



that, but then he told me he would like me to wait, that he wanted to call the oncology radiologist because of the description of microinvasive, that he thinks I should take radiation. Unfortunately, they diagnosed me in April. I did not go to Johns Hopkins until August. According to the suggestion at Johns Hopkins, I went ahead and got radiation, and I was taking Arimidex as well, and I'm still taking it. My question is, because of the time period between the time that I had my surgery and the time that I had the radiation and the medication, does it have any effect on the prognosis? Do you understand my question?

**ELYSE S. CAPLAN, MA:**

That's a good one.

**PAUL B. GILMAN, MD:**

A couple of things: One, as we mentioned earlier, is that there are some women with DCIS who might be well served with just a lumpectomy alone and no radiation. Typically, that's when everything falls into place as favorably as possible: We're dealing with a very small DCIS—low grade, grade I or, at most, grade 2; a very clear and often fairly sizable margin around it; no unfavorable features; none of the things we mentioned—the necrosis and things like that—that suggest it's more aggressive. If we have that situation, we might say, "This was a tiny, very favorable DCIS, good margin rounded. That woman may well do just as well without radiation."

Now, if we start to see unfavorable features, and in my mind we've always said that if you see a DCIS with what we call focal, microscopic invasion—focal microinvasion—it's still going to behave like DCIS. I think that's true, but now it's moving into that group of DCIS that's not as favorable, so in my mind, if you find a little bit of invasive cancer, that strengthens the argument clearly in favor of radiation.

The other question is, what about hormonal therapy? Well, Arimidex is something that would be used. First you have to ensure that we're dealing with a postmenopausal woman, because the aromatase inhibitors can only be used in post-, not pre-, menopausal women. . . . One could argue that because we've got a little bit of invasive cancer, if we're dealing with invasive cancer more and more these days, we are using the aromatase inhibitors as opposed to tamoxifen. So I think maybe a little more of an argument [could be made] to say that tamoxifen is reasonable. [However,] Arimidex is reasonable. Because of the invasive component,

that starts to change even our systemic recommendation a little bit. So reasonable.

Timing-wise, one study a number of years ago in Boston at the Joint Center for Radiation Therapy [http://content.nejm.org/cgi/content/abstract/334/21/1356] suggested that if women with early-stage invasive cancer went more than eight weeks from surgery to starting radiation, they had a significantly higher risk of local recurrence. It really hasn't held up over the years, partly because those women with invasive cancer are often delayed because they're getting chemotherapy, which probably has some benefit. The difference and the concern over the years really hasn't held up.

We don't like to delay too long. If we're talking about a year's delay, obviously we'd question whether it even made sense to go ahead with the radiation at that point. But if we're talking about a few months, it still is not unreasonable. I think six months is getting to the outer fringes. Have we treated patients like that in our experience with our radiation oncologists? We have. It's an uncommon occurrence because a lot of things have to happen to make that develop. But it doesn't eliminate the benefit of the radiation.

Regarding the hormonal treatment, particularly because we're talking about preventing not only recurrence but also a new cancer, in some ways there's an argument to be made that we have even more room and more flexibility. Many, many years ago, when we first started using tamoxifen in node-negative invasive breast cancer, there were a number of women who had been diagnosed and not treated with tamoxifen because it wasn't the standard. Then, a year, two years later, when new data came out, they started tamoxifen. We know that for women who are on tamoxifen, complete that, and go on to letrozole, or Femara, there is a benefit there. And we know that even if it's started in much delayed fashion, there's still a benefit. I think, given the intent of the hormonal treatment and some of that information, you've got even more room there. I'd feel even more comfortable saying the six months wouldn't bother me in terms of the benefit of the hormonal therapy.

**WOMAN:**

In 2000, I was treated for DCIS with a lumpectomy and radiation, five years of tamoxifen. I think in about 2004, also osteopenia, so they put me on Fosamax. Now I'm reading that Fosamax caused osteonecrosis of the jaw. My general physician put me on Fosamax, and my

gynecologist is saying to maybe think about Evista. What I've known is that tamoxifen is going to cover me for more than five years of taking it, so now I'm not sure what to use for osteopenia. Stay on my Fosamax, or switch over to something—Evista, which another doctor is suggesting?

**ZONERA A. ALI, MD:**

Evista, we know, at this time will not be of any harm to you. To tell you the truth, that study has not been done, but it will only help as far as your estrogen status is concerned. We are not aware if suppressing estrogen for more than five years is harmful. The reason we ended up using tamoxifen for five years and not beyond that was because when we did carry it beyond five years, there was a higher risk of uterine cancer. That's the reason it was five years, how we came up with a magic number of five years. With Evista, there is no risk of uterine cancer. Truthfully, if your gynecologist thinks that will be a better option for osteoporosis—and you're right, osteonecrosis of the jaw is one of the complications of bisphosphonates—from your breast cancer point of view, it should not be of any harm at all. It could only help it.

**ELYSE S. CAPLAN, MA:**

A question over here.

**WOMAN:**

I have one question and one, hopefully, answer. (Laughter) The lady who said she had the pain, one of the cards in the bag talks about [physical therapist] Richard DeMaria. I'm a former patient of his, and he is excellent. I really recommend that you take whatever time, money, effort you can to go see him, because he will work with that and a whole lot more. You'll be quite surprised at the difference.

The question I have is, in all these years, I had DCIS diagnosed in '98. I had surgery, reconstruction, chemotherapy and radiation, so I guess I'm at the extreme of DCIS that is bad. However, I'm still here, and apparently they're surprised at that, so it wasn't that bad. (Laughter) Or something worked. My question is, all these treatments I had are almost the same as everything you've said except for one thing: Nobody I have ever met has been given Fareston, and that's what I had instead of tamoxifen. I don't know if it's like tamoxifen, if it's an aromatase inhibitor or what it is—no one seems to be able to tell me— but whatever it is, that's what I went on.



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## **PAUL B. GILMAN, MD:**

Fareston – and the generic name is “toremifene” – came out several years ago. It is virtually the identical drug to tamoxifen. The thought was that it had less effect on the uterus, so the thought was that toremifene, or Fareston, might be better than tamoxifen because it wouldn't pose the risk of uterine cancer, and it came out around the time that the information really started coming out about tamoxifen and the risk of uterine cancer. The mechanism of action is the same as tamoxifen. We were part of a large study [http://www.ncbi.nlm.nih.gov/pubmed/15550579] that was completed some years ago that compared tamoxifen with toremifene, or Fareston, and women were randomly assigned to one or the other. It wasn't a double-blinded study; we knew what they got.

At the time, I know our surgical oncologist was very keen on the study. My feeling was that it was a very uninteresting study because it was really the same drug, two different versions of it. The difference in terms of uterine cancer was very small. Truthfully, the reason I encouraged women to go on the study was that the drug was provided for them, and at the time – the prices over the years have come down, but tamoxifen in those days was a relatively expensive drug. This way, a woman could get tamoxifen or Fareston – we knew which one; we knew they were the same drug – and get it for free. It was a reasonable study just to basically get the drug that way.

Because the worldwide use of tamoxifen has been so wide – thousands and thousands of women – and tamoxifen goes back to the 1970s in terms of the early trials and the first use of it, I think Fareston just didn't have enough about it to make it different and stand out so it just really never caught on. It's a very reasonable drug. I view it as every bit as effective as tamoxifen, but it just never caught on.

## **WOMAN:**

Hi. Seven-and-a-half years ago, I was diagnosed with early-stage breast cancer, and I went through chemo and radiation, etcetera. At one time, I had a [re-excision], and in the pathology report it showed that they found a small spot of LCIS. I asked my oncologist, “What does it mean?” He said, “Oh, it means that you're at higher risk for breast cancer in the opposite breast,” which alarmed me. He said, “But we're not concerned about that, because we already know that, because you've had breast cancer.”

Well, seven-and-a-half years later, I was recently, just a few months ago, diagnosed with breast cancer in my opposite breast. It's early, stage I, and I should be fine, everybody's telling me. Again I'm going through the chemo, and they're recommending radiation and a hormone again, but in the back of my mind, because of that LCIS, I'm scared that I'm just at a very high risk to have this and maybe I should do the prophylactic mastectomies. I've had genetic testing done recently, and I do not have the gene. Is there any advice you could give me, or any comments?

## **ZONERA A. ALI, MD:**

It is a tough question and a tough situation. It is often a personal decision. We know what LCIS can do. It can definitely present with cancer in the opposite breast. One thing I can tell you is that once you have had radiation and lumpectomy, the likelihood of developing cancer in the treated breast becomes much, much smaller. That's where we ended up treating patients with lumpectomy and radiation and stopped doing mastectomy. If it is of any assurance to you, having had lumpectomy and then you're going to get radiation to that breast, your risk is going to be much lower than what it was for an untreated breast. The comfort level often is a personal thing. I have to say, and sometimes that doesn't happen until you have had mastectomies. Do you have family history, too?

## **WOMAN:**

[Inaudible]

## **ZONERA A. ALI, MD:**

But you are the type of person for whom a bilateral mastectomy is recommended, something which is not unreasonable at all.

## **ELYSE S. CAPLAN, MA:**

One of the things I'd like to highlight from what you chose to share is that you sought genetic counseling and testing. I want to underscore that and highlight that in some of the more complicated situations, or if you feel your case or your family history is more complicated, genetic counseling and testing can be a really important thing for you to do to help take charge of your health, to learn as much as you possibly can that medicine has to offer, to help give you insights into some of these really challenging decisions that we all have to make.

## **WOMAN:**

I have DCIS questions. I was diagnosed about seven weeks ago with it. I've had two lumpectomies. Neither one of them have come back with clear margins. When I first got the diagnosis, I was like, “Oh, we'll go in, we'll get clear margins. You may not even have radiation.” Then, when we did get clear margins, it was, “Well, we'll go in. But then we'll do the MammoSite.” And, “Oh, I can deal with this. This is no problem.” Then that one comes back, and it's not clear margins. And I'm still waiting.

Next week I'm going to meet with a medical oncologist and the radiologist, but in my mind, I'm sort of having a problem dealing with this. I have a non-life-threatening-type disease here. Why do I have to go through a mastectomy? Yet, in my Van Nuys chart [prognostic index] I'm a ten, so I have a more aggressive type. So, what is the percent? Is there a percentage of what are my chances of it going into invasive when I'm that high, as opposed to a three, a four?

## **PAUL B. GILMAN, MD:**

I think the risk still remains low, but I think the risk of developing an invasive cancer could certainly be at least in the 10 percent range, could be approaching the 15 percent range with longer follow-up. The higher the score, what that tells us is, probably, the greater the recurrence risk, but it also tells us, probably, the greater the need for radiation. One of the things in all of the clinical trials that have been done is that every woman with DCIS, no matter what the specific features of her DCIS were, benefited from radiation. There's no group that didn't have some benefit.

On the one side, that means even women with very favorable DCIS who might be served without radiation still could derive some benefit, and women with very unfavorable DCIS clearly still derived significant benefit. There is the risk, and I think the key is to treat this as effectively as possible to prevent a recurrence, simply because the recurrence could be an invasive cancer.

In a sense, DCIS is not of itself a life-threatening disease, and that is true. It's not going to metastasize. It's not going to impact on survival unless it becomes an invasive cancer. The goal is to keep that from happening, because invasive cancer is a potentially life-threatening problem. Really, the key to the treatment of DCIS is doing what's most effective to prevent it from recurring. If that can be accomplished with just a



lumpectomy, that would be fine; if it means lumpectomy and radiation, and sometimes it does mean mastectomy, to really reduce the risk down to that acceptable level, ideally below 10 percent.

**WOMAN:**

My question may be redundant. When you're talking about DCIS, it's generally diagnosed, localized to the milk duct. If there is an invasive component to that, that's when you're talking about it becoming more aggressive. It can spread to different parts of the breast tissue. When is that diagnosis made that it's invasive? Is that done at the biopsy, or is that done when you're doing the surgical component, doing the lumpectomy?

**ZONERA A. ALI, MD:**

As Dr. Gilman said, sometimes the first test will be something called fine needle aspiration, where they basically take out some cells. When a pathologist is looking at – they see some cells that are just floating in space that look abnormal. Often that is followed by something called core biopsy. In core biopsy, they actually take the tissue out, and there you can see the intact structure of the breast tissue. Often at that time, depending on how big the core biopsy is or how big the tumor is, they're able to make the diagnosis of DCIS, DCIS with microinvasion or DCIS with invasive cancer, because there you have enough tissue to be able to do it.

However, in some people, when we have a tumor that is, for example, 5 centimeters in size, when you're doing a core, it's very small. It's normally less than 1 centimeter in size, so it might be the sampling where the tissue that you got just showed DCIS, but there might be invasive cancer. It's not uncommon for us to find invasive cancer in the final pathology when they've gone and done a whole resection of the tumor.

**WOMAN:**

[Inaudible] as the diagnosis is made from – it's in the duct, and it's only in the duct. That's a totally different treatment versus as soon as that cell goes out of the duct. That changes your whole course of treatment, because if it's only in the duct, you simply remove that area. If it didn't go into the tissue, you don't need the radiation, any of the chemotherapy, the tamoxifen. You don't need any of those. Is that generally the standard?

**ZONERA A. ALI, MD:**

No.

**WOMAN:**

No?

**ZONERA A. ALI, MD:**

No, no, no. That's where we are getting a bit confused. For DCIS, which is when it has not gone beyond the ducts – it has not gotten into the deeper tissue – we know that the tissue left behind is going to develop into breast cancer, invasive breast cancer, so what we want to do is take it out. That's the excision. But we know that there's a high risk of developing DCIS in the rest of the breast, so we give radiation to people who have DCIS. Then, for people who have DCIS, there's a higher chance of developing it in the opposite breast, so we recommend, depending on the grading and all, tamoxifen for such people.

The main difference between invasive and DCIS is whether we are going to look at the lymph nodes. Unless the DCIS is high grade, normally we do not look at the lymph nodes. Also, the other difference is, depending on the size, we would often do chemotherapy. Tamoxifen, raloxifene – they are all called hormonal therapy. They're actually against hormones, but they're called hormonal therapy. Chemotherapy often is drugs that are given intravenously for treatment of invasive cancer to prevent the cancer from coming back. When we think the chances are higher than what can be dealt with with hormonal therapy, we would do chemotherapy. We do not do chemotherapy for DCIS, but for invasive cancer, it's something we would entertain.

**PAUL B. GILMAN, MD:**

I think the one other distinction – because you'll see this in pathology reports – is did we find an invasive cancer in addition to the DCIS, or was there what we call focal microinvasion? What that means is if it's an invasive cancer in addition to the DCIS, the area has been removed, and we say, okay, we removed a tumor that measured 1 centimeter, and of that, 5 millimeters was a DCIS and there was a 5-millimeter invasive cancer. Again, sometimes you don't know that until the lumpectomy, because the core biopsy is only a small sampling.

If they did the lumpectomy and they saw what they call "focal microinvasion" – that means in one spot or maybe a few little spots; there are just a few little cells that have invaded – that still tends to behave like DCIS. We would do a sentinel node biopsy because there's an invasive component. As a precaution, we would do a sentinel node biopsy. In terms of treatment, we would still view this as a DCIS and treat accordingly, which would mean

radiation, tamoxifen possibly – it still would not mean chemotherapy or any more extensive surgery. It's important to distinguish, if there is invasive cancer, how much invasive cancer.

**WOMAN:**

Are they two different kinds of cancer? Or is it the same cancer; it's just spread?

**PAUL B. GILMAN, MD:**

It's basically felt that if you look at the cancer cell – and there have been studies that have actually looked at genes within these cells and have found that you can see a gene abnormality way back when you had just proliferating changes. There is what we called atypical duct hyperplasia, where the cells lining the milk duct have started to overgrow, or atypical lobular hyperplasia, where the cells kind of at the end of the milk duct into the lines have started to overgrow, and they look abnormal but don't meet the criteria to call them malignant or cancer.

What is felt happens next is that you then move to DCIS, ductal carcinoma in situ. Now the cells are proliferating. They're still not getting past that wall that we talked about into the surrounding tissue, but they're felt to be clearly malignant cells. Then, finally, we feel that what happens next is those cells become invasive. Something else happens within that cell that it now starts to grow, not only proliferate, but grow beyond its boundaries, and it starts to get through that wall.

It's kind of like if all of us were ductal cancer cells sitting in this room, which is the milk duct, this is a DCIS. If some of you along there just started to kind of break your way through that wall into the other room, that would be an invasive cancer. It's all sort of a continuum of the same cancer. It all starts early on. You can trace certain genetic abnormalities in those cells that you see, in that very early thing, the DCIS, the same genetic abnormality, which suggests that it just sort of starts here and then works its way through.

**WOMAN:**

Thanks.

**WOMAN:**

Thank you. A clarification and then a question: Did I understand you correctly earlier, that invasive LCIS is always ER/PR negative?

**ZONERA A. ALI, MD:**

Positive.

**WOMAN:**

LCIS, invasive – it's always positive.



# LIVING BEYOND BREAST CANCER®

L B B C . O R G

## ZONERA A. ALI, MD:

Yes.  
[Inaudible Portion]

## ZONERA A. ALI, MD:

LCIS is not invasive.

## WOMAN:

But you could have LCIS that has turned into an invasive cancer, though, correct?

## ZONERA A. ALI, MD:

LCIS is a marker for developing invasive breast cancer. Remember how Dr. Gilman was talking about DCIS being different stages of what eventually could become invasive cancer? If a lesion has LCIS, it is not going to develop into cancer itself, but what it does tell us is that around that area, in the opposite breast, too, such people are at a high risk of developing invasive cancer. Do you understand? It's a bit hard sometimes to differentiate that.

## WOMAN:

I thought I heard that invasive lobular cancer is always ER/PR negative, but that's not what you said.

## ZONERA A. ALI, MD:

No, lobular carcinoma in situ is normally opposite. It is estrogen- and progesterone receptor positive. It only grows if you have estrogen.

## WOMAN:

So there is a connection then between estrogen and lobular carcinoma in situ.

## ZONERA A. ALI, MD:

That's right. Exactly.

## WOMAN:

How uncommon or how common is it for someone to have a diagnosis of both DCIS and LCIS? Thank you.

## ZONERA A. ALI, MD:

It's not uncommon. That's why, when somebody has had LCIS, we don't want just to have a few cells or aspiration and say, "This person has LCIS and we do not need to do something with this person," because that is telling us that that particular person is at a high risk of developing invasive breast cancer or DCIS. That's the reason for increased surveillance in such people.

## WOMAN:

In light of what you just said, I had LCIS when I was premenopausal. I went on tamoxifen. I'm now on raloxifene, and my question was going to be whether I should go for BRCA testing, because my mother had cancer. We don't know what type. It was breast cancer. My daughter is now 34, and she said, "Mom, do you think you should get tested?"

## ZONERA A. ALI, MD:

You should. You were young when you were diagnosed with breast ...

## WOMAN:

No, not really.

## ZONERA A. ALI, MD:

Premenopausal.

## WOMAN:

I was right on the cusp of menopause.

## ZONERA A. ALI, MD:

It's unbelievable when you talk to a genetic counselor the way they ask you a question; you remember so many other relatives who can have breast cancer. Sometimes just talking to them also reassures you that maybe this is not one of those hereditary cancers. But whenever we see a new patient, we often go over their history, and having had a mom with breast cancer and then having yourself had breast cancer, yes, that would be considered something where you should seek genetic counseling.

## WOMAN:

Should you change your diet if you have LCIS? Does diet have an effect on it?

## ZONERA A. ALI, MD:

Not that I am aware of, and I'm going to ask Dr. Gilman to correct me if I'm wrong about it. To tell you the truth, I cannot remember. One of the things, I guess, is the soy. There is always that question about soy changing to estrogen in the body. We have soy in every food, so if you start looking, you won't eat anything. But there are these things called soy capsules that are very rich in just soy, and often I tell people to avoid them because they could eventually change to estrogen, and that could then contribute to it. A lot of times, our body is producing estrogen, especially in premenopausal women. That is the main source that drives these tumors themselves, and there is not much we can do about it. The short answer is, there has not been any benefit [seen] from changing the diet.

## PAUL B. GILMAN, MD:

It's a debate that has gone on for years, and there's always been a concept that there is some relationship. For example, years and years ago, there was talk that if you looked at Asian populations, let's say, particularly Japanese, who followed a traditional Japanese diet, they tend to have very low incidence, [ultimately] speaking, of breast cancer. Then, if you see the population that moved from Japan to the United States and over a couple of generations started to change that diet, the breast cancer incidence started to change. There was always some concept that a low-fat diet might be beneficial. There has been some argument that soy might have some protective effect.

The one study that showed a benefit to the low-fat diet was an interesting one a couple of years ago that looked at women with early-stage breast cancer getting chemotherapy – protective or what we call adjuvant chemotherapy. One group had a normal diet; the other had an intervention to follow a low-fat diet, not an extreme low-fat diet, but kind of a reasonable one, with some nutritionist intervention. That group seemed to do better, with the chemo plus the low-fat diet versus the chemo alone, as far as breast cancer recurrence.

One of the areas of real interest right now has to do with vitamin D levels and the concept that vitamin D may have a protective effect against breast cancer, so that women who are vitamin D deficient might be at increased risk and supplementing vitamin D might be helpful. What's unclear there, I think, is whether it is really helpful, and how helpful? And if you're going to supplement vitamin D, are we talking about bringing deficient levels up to normal, or are we talking about high levels and bringing normal up to super normal? Most of the discussion right now probably centers more around vitamin D deficient and correcting that, bringing it up to normal.

There was a study a few years ago that looked at changing our diet from the trans fats and saturated fats to unsaturated fats, which is beneficial for the heart effects, so it's certainly worth doing for that reason. There was some concern that if we modify the fat in our diet, will it benefit the heart in women but be detrimental for the breast? There was at least one large study that suggested it was not detrimental, at least, for breast cancer. So, I think the diet issue remains unanswered and still debated, but it probably has some impact.



**WOMAN:**

I was diagnosed with DCIS last December, this past year, at 50, and I'm premenopausal. I had a lumpectomy and did no other treatment. We did a re-excision to clear the margins, and they were clear, but the pathology report also found that I had LCIS and atypical hyperplasia, so this last mammography that I had, they also did an ultrasound. You never spoke about ultrasound, and I didn't know what role that is, other than getting an MRI, because I've never had the MRI.

**ZONERA A. ALI, MD:**

Ultrasounds are not used themselves for surveillance, and one of the problems is that the breast is a large organ. Just to be able to do that type of ultrasonography will take a long time, and to interpret would be different. Ultrasounds are often used in conjunction with mammography. If there is something that looks suspicious, that doesn't look right, you can do the ultrasound of that area. The way it looks on the ultrasound – how dark it is, what type of a flow it is – helps in determining whether this needs to be further classified. All of us have cysts, which are benign things. Most of the cysts are benign, and they can look abnormal sometimes on the mammogram, and ultrasounds are very helpful, for example, in differentiating those.

Ultrasounds themselves are not used for surveillance, but with regards to whether there is something on mammogram, they do help in defining such lesions. In people who are at high risk, including people with LCIS, there is the role of doing MRIs to pick up early-stage breast cancer. Has it been proven yet? Not yet. But a study that looked at people with BRCA1 and BRCA2 – the genetic markers, often an increased risk of breast cancer – out of the Netherlands and Europe basically did show that if MRIs were done, the invasive breast cancers were picked up earlier than the mammograms.

The problem with MRI, which I think we need to tune out better, is it picks out a lot of nonspecific things, so many people are put through biopsies for benign lesions, and I think that's where we need to learn how to be able to differentiate better what is invasive, what is noninvasive. Then I'm sure it will become more and more common.

**ELYSE S. CAPLAN, MA:**

I wish we could get to the very last question. Maybe on the way out, a couple of you who haven't asked a question can actually take that opportunity, but our night must come to a close. I want to thank all of you for hanging in there at the end of your long day. I really appreciate the excellent questions that all of you brought to add to our program. It really does help us get so much more information out. Please keep in mind that your blue evaluation forms are in your bags. They're double sided. Again, let us know what you're interested in and how we did tonight. And safe travels home.

I have to thank Dr. Gilman, coming out with laryngitis/bronchitis, and Dr. Ali for joining him at the last moment to sort of tag-team and co-present. (Applause) Together you covered an awful lot of territory, and I appreciate you coming out at the end of your very long day. Thank you so much. I really appreciate all of your time. Safe travels home, and stay in touch.

**PAUL B. GILMAN, MD:**

Not to hold everyone, but just one second. I just want to especially thank Dr. Ali. It's wonderful to have her as a colleague, somebody this knowledgeable and this helpful and even helpful to me directly. I also want to say that this evening was a great experience for us and reminded me how much I thoroughly enjoy working with Living Beyond Breast Cancer. It's an amazing organization with amazing people like Elyse, who I've known for a number of years, Kathleen, and the work that they do and what they provide for women is just beyond words, so thank you very much for having us here this evening. (Applause)

**ELYSE S. CAPLAN, MA:**

Thank you. It's always nice to hear that from such an esteemed medical oncologist, so we really appreciate that.

[END OF TRANSCRIPT]