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Triple-Negative Breast Cancer: Research and Treatment Update

April 18, 2008

Lisa A. Carey, MD, ScM

OPERATOR:

I would like to welcome everyone to the Living Beyond Breast Cancer conference call. Thank you. It is my pleasure to turn the floor over to your host, Elyse Caplan. Ma'am, you may begin your conference.

ELYSE S. CAPLAN, MA:

Thank you. I'd like to welcome everyone to LBBC's teleconference: "Triple-Negative Breast Cancer: Research and Treatment Update." My name is Elyse Caplan. I am the education director for Living Beyond Breast Cancer, and I'm happy to serve as the moderator for today's program. I am especially pleased to announce that this program was truly a collaboration between Living Beyond Breast Cancer and the Triple Negative Breast Cancer Foundation [<http://www.tnbcfoundation.org>], with general support from Susan G. Komen for the Cure [<http://www.komen.org>]. This partnership has enabled us to reach many more women living with or concerned about triple-negative breast cancer so we can educate and support so many people today and beyond today through an audio replay of the program.

In a few minutes, I'll introduce the chairwoman of the board of the Triple Negative Breast Cancer Foundation so that she can make some opening remarks. A few housekeeping things I'd like to run through: Today's topic is of great importance to many women we hear from throughout the year affected by breast cancer. We wanted to ensure that tailored information on different subtypes as well as different stages of breast cancer is presented throughout the year in our programming. This is our first teleconference on the subject of triple-negative breast cancer, and we look forward to presenting updates on a regular basis.

Our featured speaker today will be Dr. Lisa Carey of the University of North Carolina, and you'll hear a little bit later from her on the latest medical and research updates to empower you to

ask questions of your own healthcare team that can apply to your situation. . .

. . . To get down to details, we will have a presentation, and at the end of the presentation, we'll have a question-and-answer portion. I'm pleased to welcome Hayley Dinerman, chairwoman of the board for the Triple Negative Breast Cancer Foundation. We thank Hayley and everyone connected with the foundation for all of the support and all that they do on behalf of people living with triple-negative breast cancer. Please welcome Hayley.

HAYLEY DINERMAN:

Thank you, Elyse. On behalf of the Triple Negative Breast Cancer Foundation, I'd like to welcome you to this very important conference and to thank Living Beyond Breast Cancer for taking the initiative to organize this event. I'd also like to thank Susan G. Komen for the Cure for making this possible through the generous support.

It's now my pleasure to introduce one of the Triple Negative Breast Cancer Foundation's medical advisers, Dr. Lisa Carey. Dr. Carey is an associate professor in the University of North Carolina Department of Medicine's Division of Hematology and Oncology. She has served since 2003 as the medical director of the UNC Breast Center and is the UNC Lineberger Comprehensive Cancer Center Protocol Office Executive Committee Breast Disease Group leader as well as the UNC LCCC Protocol Review Committee Breast Cancer chairwoman.

Dr. Carey has an interest in clinical and translational research in breast cancer, with a particular interest in the clinical implications of different molecular subtypes of breast cancer. She designs and leads clinical trials and often works with laboratory investigators. Dr. Carey has served on the American Society of Clinical Oncology Program Committee and as faculty for the ASCO annual meeting for several years. She was named

to the Cancer and Leukemia Group B Breast Cancer Committee in 2003. She was also awarded a Doris Duke Clinician Scientist Award in 1999 and a Career Development Award from the National Cancer Institute in 2000. Dr. Carey, it's an honor to have you here with us today.

LISA A. CAREY, MD, ScM:

Hi. Thank you, everybody. I very much appreciate you taking time to join us, and I hope it will be educational for all. I've been asked to take a few very brief moments to talk about the nature of triple-negative breast cancer and the clinical implications of it and the implications that having this particular disease has for treatment.

I will start with the first order of business – just talking about what this disease is. We discuss "triple-negative disease," which means that the three proteins that we test for routinely on breast cancers – ER, or the estrogen receptor; PR, or the progesterone receptor; and HER2 – those assays are all negative. That's where the name comes from. That, of course, means we have fewer choices for treatments, because the targeted therapies that have been developed so far, that we know work particularly in early breast cancer, are ones targeting ER, PR and HER2.

But . . . many of you who have done some reading on this have noticed that there is a lot of discussion about what exactly it means to be triple negative. Part of the interest in this subtype comes from our understanding of the underlying biology of the disease, and that biology has been defined by scientific methods that go well beyond just triple-negative status. These are scientific methods that look at sort of the molecular portrait of the cell and all the genes of the cell, not just three of them.

The subtype that the triple-negative breast cancers mostly overlap with is a subtype called the basal-like subtype, and some of you may have seen that name used sort of alternating with triple negative. But it's important for us to remember



that scientists will talk about the basal-like subtype of breast cancer, which is something we can test for in the laboratory but can't test for in the clinic. Clinicians will refer to triple-negative breast cancer, and those two things mostly, but not entirely, overlap. So when we talk about triple-negative breast cancer, we're mostly talking about the basal-like molecular subtype, but not entirely.

That's sort of the "what's in a name" part of this. I think over the next few years we'll get far more sophisticated about these ways of identifying the biology underneath a particular kind of breast cancer, but we're only partway there right now. So, forgive me: I will use the word "basal-like" whenever I'm talking about something that has been done where they actually were able to look at the underlying biology, and I'll try to use "triple negative" only when we're using the clinical assays – the things that we actually have available to us when we're deciding treatment.

The basal-like subtype of breast cancer is a kind of breast cancer that was identified when scientists, who had these new technologies that let them ask questions about thousands of genes simultaneously, getting a real molecular picture of a cell, went through a bunch of breast cancers and said, "Are there different subtypes of breast cancer?" The short answer is, yes, there are subtypes.

In fact, breast cancer is not one disease. It's actually a family of biologically distinct diseases. One of them is this basal-like subtype, and this has been confirmed in several different laboratory investigations. You can see this characteristic type of breast cancer, whether you look at genes or whether you look at proteins, or pretty much whatever way you use, it does come up over and over. It's quite a characteristic and reproducible thing. That's important, because once you know that you're finding something that's reproducible, you can start looking for variations in risk factor and behavior and treatment options.

The characteristics of this particular subtype are that it's – of course, as you would predict, the group of genes that relate to hormone receptors, like estrogen receptors and progesterone receptors, are typically low. Also, the group of genes that relate to HER2 are typically low. This fits with why we see ER, PR and HER2 being low. There is another cluster of genes that we call the basal cluster that is characteristic of this particular kind of breast cancer, and they're high. There are a number of them, which I'm going to talk about later.

The genes themselves are not particularly relevant. It's more [relevant] that we can identify a group of them that are up, and a few of them we may be able to someday target with drugs. Another characteristic thing, if you look at the genes expressed in basal-like breast cancer, is that the genes that are related to how quickly a cancer grows tend to be high, so this is considered a very proliferative cancer, which fits with what we see clinically.

People sometimes wonder, when we look at these subtypes and different biologic kinds of breast cancer and other cancers, whether this is something that evolves. Do you start as one kind and turn into another kind? . . . Breast cancers do change over time from when they first are diagnosed to when – if – they come back. There are differences that are probably relatively subtle. If you look in a global sense of subtypes, like the basal-like subtype, we do see it.

If you look at the breast cancer that was first diagnosed, and then you look at the same woman's liver metastasis several years later, typically these two things will look more or less the same, and they will both be basal-like. Occasionally you do see some shift, but usually not. In addition, we see evidence of these kinds of subtypes even in the precancerous lesions called ductal carcinoma in situ. It looks like it's there very early, and it's there at the end. So, not only are they characteristic across different groups of women from different countries and different treatments, but they're also characteristic throughout the life of the cancer.

Now, some of you may know that we got involved in trying to translate this finding of different subtypes of breast cancer to the clinic several years ago when, of course, the scientists were finding these different types. We weren't quite sure what it meant in the clinic, so we went to our colleagues here. I'm from the University of North Carolina, and we have a very famous School of Public Health. We went to Bob Millikan, who runs a very large study looking at breast cancer risk factors, in which they had routinely collected a whole bunch of the tumors that go along with the women participating in the trial, because they were looking not only for traditional risk factors for breast cancer but also for genetic risk factors.

We went to Dr. Millikan and his colleagues and asked if he could help us figure out what the different characteristics were of the tumor subtypes and give us a little sense of how common they are. The Carolina Breast Cancer Study

[<http://cbcs.med.unc.edu>] is particularly interesting because the people who designed it in the early 1990s recognized that we don't get enough information about risk factors of any kind of breast cancer in African-American women and in young women. Because of that, they designed the trial so that it would over-represent those two groups so they could try to figure out whether there were differences in premenopausal breast cancer and in breast cancer in African-American women compared with breast cancer in postmenopausal, Caucasian women.

We went to the Carolina Breast Cancer Study tumors and did subtyping, using a protein approach, and it turns out that all of the subtypes that were found in the scientific investigations, in fact, were found in the North Carolina samples, and the basal-like subtype made up 15 to 20 percent of them.

There were some clinical characteristics that seemed to go along with it. When you look under the microscope, these tumors are virtually always what we call invasive ductal carcinomas. Sometimes they're invasive ductal carcinomas with some lobular features, but they are virtually never invasive lobular carcinomas. There are some other histologies that we do see sometimes, but they're relatively uncommon. They're almost always high grade, and one of the things that we wondered was whether they tended to come up at different stages. Would there be more or less stage I, stage II, etcetera, or nodal involvement? We didn't see a lot of difference there.

I mentioned the Carolina Breast Cancer Study oversampling and over-representing African-American women and premenopausal women by design, and because of that design we got some very interesting information about an interaction between basal-like breast cancer and race and age. We found that the basal-like subtype seems to crop up, as I said, about 15 percent of the time; about 15 percent of breast cancers are this particular kind, with one notable exception.

That exception was that young women, meaning premenopausal, who were African-American were twice as likely as everybody else to get this particular subtype. Their rate was just shy of about 40 percent in this particular study, which is not to say they have a higher risk of getting breast cancer. In fact, the risk in African-American women is lower than in Caucasian women overall. But if they got it, they were more likely to get this particular subtype.



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That finding has been shown not only in the North Carolina data set but also in other data sets around the country, suggesting that there is something real there. The obvious question is why would this happen? Why would there be a higher propensity to develop this subtype for those who are young or African-American? We don't know the answer to that, but that gives us a direction to look in as we go for prevention studies.

If one group that is more prone to getting basal-like breast cancer is young, African-American women, there is another group that we know a fair amount about: women who carry inherited mutations in the gene BRCA1. Many of you may have heard of what we call familial breast cancer, which is uncommon. It makes up 5 to 10 percent of breast cancers overall. But those who carry one of these inherited mutations for familial breast cancer have a much higher risk of getting breast cancer: between 50 and 90 percent over a lifetime, which is much higher than the average woman.

Women with BRCA1 mutations, when they get breast cancer, most of the time get this basal-like subtype of breast cancer. Two questions go along with that. The first is why, and we don't know the answer, but that gives us a direction to look in from a scientific standpoint. The second is what does this mean therapeutically? I'm going to talk about that a little more later.

One of the things we think about when we talk about risk factors for breast cancer is the traditional risk factors. It's been long known that breast cancers that are hormone receptor positive seem to behave differently from breast cancers that are hormone receptor negative. That plays out in traditional risk factors, too. This recognition actually predates the subtyping studies I've been talking about.

The Nurses' Health Study [<http://www.channing.harvard.edu/nhs/>] – which, many of you know, has given us a ton of information about risk factors for breast cancer – went back a few years ago and looked at the women who got breast cancer. They took their traditional models and separated out the cancers by ER-positive breast cancer versus ER-negative breast cancer and found that some of the classic risk factors – for example . . . the standard dogma is that women who have never had children have a higher risk of developing breast cancer than women who had many children.

That's certainly true, but only for hormone receptor-positive breast cancer. That relationship seems to be less when you get to hormone receptor-negative breast cancer, which I think speaks to the fact that as we recognize that breast cancer itself is not just one disease, we have to go back and rethink how we ask the question of what causes breast cancer, because the answer may be very different for a hormone receptor-positive subtype or a hormone receptor-negative subtype – or, in fact, it may be different for a basal-like subtype than for everything else.

A couple of studies have started to try to do this, and they do find that the effect of traditional risk factors seems to be very different in basal-like breast cancer compared with hormone receptor-positive subtypes, for example. That's important, and that's something for you all to keep in mind as you go forward and start hearing about some of these studies that are being done, because they are possibly modifiable. We may be able to find that certain subtypes are much better prevented by something that you can do – activity, diet, breastfeeding, things like that. It's going to be very important for us to see if we can figure out who is at risk and then figure out, among people who are at higher risk of getting, for example, the basal-like subtype, things they can do to try to reduce it that are simply lifestyle changes and don't involve surgery or drugs.

What about behavior? All of these subtypes were developed not in order to define prognosis or to define treatment, but were simply defined by being different from one another. Many of you know that there are a whole bunch of prognostic profiles that we use in the clinic now. This is a hot area in oncology, because these genetic profiles can help us decide whether a cancer is going to behave more or less aggressively and sometimes help us decide treatment. Of course, that doesn't tell us about the basal-like subtype.

If you look at these prognostic signatures and compare them to the subtypes, it turns out that these prognostic signatures will generally predict that the basal-like subtype is a more aggressive type of breast cancer. In truth, the original data sets – which are all historical, so many of them are several years old – generally find that the basal-like subtype and, in fact, the other ER-negative subtypes, seem to have a worse prognosis than the hormone receptor-positive subtypes.

In particular, the relapse rate tends to be a bit higher for these. It's a little more frequent, and it's a little bit earlier. In fact, there is sort of a peaking of relapse, somewhere around two, three, five years after diagnosis, with a very quick kind of dropping off of risk as you move along in time. When you get out to seven, eight, nine, ten years or beyond, the risk of relapse for basal-like subtype is actually less than that for hormone receptor-positive breast cancer, for example. So, the risk tends to be early, not later.

That's important because chemotherapy primarily affects early relapse, and there have been several studies that suggest that the advances that have been made in conventional, regular chemotherapy – as many of you know, chemotherapy today is totally different from chemotherapy ten years ago, and there have been a number of very substantial advances in the way we give chemotherapy and the drugs that we use. It looks like those advances have probably benefited the triple-negative subtype of breast cancer as much as, if not more than, anything else. That's why I say these are historical data sets, and that's important, because with modern chemotherapy the prognostic implication all by itself of being triple negative is not clear.

Let's talk a little bit about the treatments. For early breast cancer: 95 percent of the patients we have are diagnosed at an early stage, when we're giving medications in order to try to prevent relapse and hopefully cure them so they live a long, full, healthy life without recurrence of the breast cancer. There is a whole group of drugs that we use in order to help prevent relapse. However, for basal-like breast cancer, because the proteins we target – ER, PR and HER2 – are not present on this subtype, we rely on chemotherapy in terms of prevention of relapse.

As I mentioned, every time we have had an advance in the chemotherapy we give – and many of you know we've gotten smarter at giving drugs like Adriamycin, or doxorubicin. We've learned that adding taxane-type drugs like Taxol, the [generic] name of which is paclitaxel, or Taxotere, the [generic] name of which is docetaxel, makes people do better. We've gotten smarter about the dosing of these things and how often we give them. Each time we've gotten smarter about the way we give chemotherapy, the basal-like subtype has benefited a little bit more than the other groups, particularly compared with the ER positive subtypes, so that's a real benefit.



Some of you may know that when a patient comes with a very large breast cancer, we often give the chemotherapy before the surgery. When we look at the response of the tumor to chemotherapy, when the tumor is still left in the breast, we see that this particular type responds very well to standard drugs. That's important, because I think there is a misconception that basal-like or triple-negative breast cancer is resistant to standard therapies. That's simply not true. It is sensitive to chemotherapy drugs of a variety of types. It's simply not sensitive to antiestrogen-type approaches or anti-HER2-type approaches.

That's part of what I'd like to impart to you about the things we know about basal-like or triple-negative breast cancer, and now I'm going to talk about some of the theories. I want to be very clear that from here on I'm talking about theoretical things that are relevant for research studies but are not necessarily something I would use in the clinic.

The first is that, as I mentioned before, basal-like breast cancer has an association with having BRCA1 mutations. That gene is responsible for repairing damage to DNA, so there is a theory that you may be able to use DNA-damaging drugs. Certain chemotherapy agents work mainly by damaging DNA, which makes the cell basically kill itself because it can't repair it, and these may be more effective in triple-negative or basal-like breast cancer because the cell's ability to repair DNA, compared to normal, is not as good.

There is a whole group of investigations that look at chemotherapy drugs that work by damaging DNA – for example, platinum-type drugs – and whether those drugs are more effective in this particular subtype compared with other breast cancers. This is not to say that these drugs are ineffective in other cancers. This is a relative thing. There is only a small amount of clinical data at this point, but certainly the laboratory studies support pursuing this in clinical trials, and some clinical trials that I'm going to talk about in a second will be directly asking this question.

The second is when we move from early breast cancer to the drugs that we use for metastatic breast cancer, it's clear that drugs that target angiogenesis have a role to play in breast cancer. When we talk about angiogenesis, that means blood vessel formation. Breast cancers and other solid tumors like colon cancer, lung cancer – any kind of cancer that's not part of the blood itself – have to grow by having the ability to grow themselves. Plus, as

they grow, they need to have a way to nourish themselves. Your regular organs have a way to nourish themselves. Your liver has blood vessels that bring in nutrients and take away toxins. For a cancer to grow, it also has to have nutrients, and it has to be able to remove toxins. That process is called angiogenesis.

There are multiple, multiple drugs that have been developed and are being developed whose main mechanism is to combat angiogenesis. These are called antiangiogenic drugs. The one that has been tested the most in breast cancer is a drug called bevacizumab, or Avastin, which was studied in a very large group of patients with metastatic HER2 negative breast cancer where they gave chemotherapy alone or chemotherapy with bevacizumab. These are women who had just been diagnosed. The women who got bevacizumab did better than those who just got chemotherapy. This is bevacizumab added to chemotherapy versus chemotherapy alone. For that reason, the FDA recently approved bevacizumab for breast cancer [Editor's Note: Dr. Carey most likely refers to clinical trial E2100: <http://clinicaltrials.gov/ct2/show/NCT00028990>. Two studies released after she spoke, called AVADO and RIBBON-1, also address bevacizumab in HER2 negative breast cancer: http://www.asco.org/ASCO/Abstracts+&t+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=34482 and <http://clinicaltrials.gov/ct2/show/NCT00262067>]

The obvious question is which patients benefited from this. They gave it to a large group of relatively unselective breast cancers. They were sort of taking all comers, except for HER2 positive breast cancer; only a handful of those were included in the study. When they went back to see whether certain groups seemed to benefit more than other groups, they found that all the groups seemed to benefit more or less equally, including the triple-negative subset.

A much smaller study using a pill form of an antiangiogenesis drug called sunitinib, or Sutent, was just reported and has some evidence of activity in a group of treated patients – those who had already had a lot of other therapies, and the cancer had grown despite them. That's another drug that's going to be tested quite actively.

Those two arenas – the idea of choosing chemotherapy for different subtypes differently and the question of whether we can select patients who are more or less likely to benefit from antiangiogenesis drugs – are the subject of a cooperative group study called CALGB 40603 [<http://www.cancer.gov/clinicaltrials/CALGB-40603>]. This is a neoadjuvant study, meaning it's for women who are newly diagnosed – not people who have already been diagnosed and had treatment, but for newly diagnosed breast cancers, where the cancer is large enough that it's appropriate to give the chemotherapy before the surgery.

This will be about 400 patients. All of them will be triple negative, and they will get either paclitaxel, or Taxol ... either by itself or with a drug called carboplatin. Then they will also either get or not get the drug bevacizumab, or Avastin. This trial is directly asking whether triple-negative breast cancer is more or less sensitive to particular chemotherapy drugs that damage DNA, like platinum drugs, and whether it's more or less sensitive to antiangiogenic drugs.

A number of other approaches are trying to take advantage of this association between BRCA1 abnormalities and responsiveness to particular approaches to therapy. I have a word of caution here: There is a great deal of interest in this because there is an assumption that BRCA1 is somehow abnormal in basal-like breast cancer. In truth, all we know for sure is that women with BRCA1 mutations – now, this is quite rare, but if you have one of these mutations and you get a breast cancer, it's more likely than not going to be a basal-like breast cancer. What we don't know for sure is, for women who don't have BRCA1 mutations, if they get a basal-like breast cancer, we're making the assumption that something is wrong with BRCA1 or other members of that pathway – the DNA damage repair pathway. That's something we haven't proven yet, but a number of drug studies are making that assumption and testing it in a direct way.

Another direction people go in is looking at whether this particular subtype of breast cancer is very proliferative and seems to have abnormalities in controlling growth. There are a couple of different ways for cancers to grow. Cancers can grow either because they grow too fast or because they don't have the normal dying-off process. Cells normally live, just like people. They are born, they live and they die. Cancers sometimes don't die



appropriately, and that's how they grow. Other cancers seem to just be very, very aggressive and proliferative, and it seems like the triple-negative or basal-like group is more often in that category where they're just growing too fast.

There are a number of drugs that target cell-growth pathways, and those particular drugs are being tested to see whether they may be more effective or particularly effective in this subtype. I point you to some trials that are ongoing, including the drugs like dasatinib, or Sprycel, and some of the PARP inhibitor drugs.

In that basal cluster of genes that are characteristic of this particular subtype are some molecules that might be drug targets themselves. For example, we talked about HER2. There is a relative of HER2 called HER1, or EGFR, which stands for epidermal growth factor receptor. That particular gene appears to be turned on and activated in basal-like breast cancers more than it is in other kinds of breast cancer. A couple of large studies have looked at whether drugs that we use against EGFR will help treat basal-like breast cancer.

There are two large trials, one of which didn't select just for triple-negative breast cancer but included a fair number of them and was reported at San Antonio last year. That's still being analyzed, but there was some reason to think that the triple-negative group that got chemotherapy plus targeting this EGFR may have done a little bit better than those who just got chemotherapy alone. There is another trial that only included triple-negative breast cancers that will be reported at American Society of Clinical Oncology cancer meetings in a month or two.

If I were to make a summary about the trials – because I'm sure there's going to be some interest in particular about these trials – I would put them in several large categories. The first category is the trials that take targeting DNA repair problems in this subtype of breast cancer as a kind of rationale and hypothesis, and those are trials that include platinum agents, platinum drugs, and a class of drugs called PARP inhibitors. There are also multiple trials of antiangiogenesis drugs, and I've mentioned bevacizumab, or Avastin, and sunitinib, or Sutent. Those are only two of a number of agents being developed that go after blood vessel formation.

As I mentioned, the EGFR or HER1 target is one that people have a great deal of interest in and is being currently studied. Finally, there is a group of drugs that are being newly formed and tested

actively right now whose role we don't know exactly in breast cancer in general, but they have to do less with the genes in terms of the genes themselves and more with how the cell controls gene expression. There are a bunch of drugs that are being developed that target [how a] gene controls or regulates the expression of drugs, which is a much more dynamic thing than the genes themselves. That's a class of drugs that I think we'll hear more about in the future.

For those of you with interest in finding out more about the trials that are ongoing for particular types of breast or other cancers, a couple of websites are relevant here. The websites of particular interest are clinicaltrials.gov [<http://clinicaltrials.gov/>] and Trial Check [<http://www.trialcheck.org/Services/>]. [Clinicaltrials.gov](http://clinicaltrials.gov) is a federally controlled website that is quite up to date, typically. Trial Check, which is managed by the Coalition of Cancer Cooperative Groups, is another way for you to do a search if you're looking for something in your area.

Those were my main summary points that I thought would highlight what people are most interested in about this particular subtype of breast cancer.

ELYSE S. CAPLAN, MA:

Dr. Carey, thank you so much for giving this excellent overview. I think a lot of questions that participants had were hopefully answered along the way. I would like to highlight the misconception you brought out, because I know that, at Living Beyond Breast Cancer, we do hear from women who identify with triple-negative breast cancer that chemotherapy is sensitive to triple-negative breast cancer. When so much information is publicly available around hormone receptor-positive breast cancer, the triple-negative women often feel isolated and are concerned about what treatments are effective for them. So I'm really pleased that you made that statement so our listeners have an understanding that chemotherapy is very sensitive for triple-negative breast cancer.

LISA A. CAREY, MD, ScM:

Yes, and that's important to highlight. That's one of the most common questions I get in my own clinic.

ELYSE S. CAPLAN, MA:

I'm sure. I also appreciated you reviewing the different mechanisms in terms of the research pipeline and highlighting the DNA repair problems and the angiogenesis, the EGFR, etcetera,

because I think that's really helpful in understanding the different targeted approaches toward improving treatment for triple-negative breast cancer, and it gives us something to keep our eye on for the future. I'm wondering: In the EGFR trials you referenced, what medications were used in those studies, for the HER1?

LISA A. CAREY, MD, ScM:

In both of the trials that have been completed, it was cetuximab, or Erbitux, an antibody drug that targets the outside of the cell where this receptor lives. But there are a number of what are called small molecules, so there are drugs that kind of grab onto the receptor and interfere with its action on the inside, and those studies are also ongoing. We don't have any reports from them.

ELYSE S. CAPLAN, MA:

Thanks. I anticipated that being a question coming up, so I thought I would ask. Thanks for clarifying that.

OPERATOR:

Our first question comes from Katonah, New York.

CALLER:

Hi. You did talk a bit about the relationship between triple negative and the BRCA1 mutation. What I understood you to say was that if you have the mutation, you're more likely to be triple negative. What do we know about it going the other way? If you're triple negative, what is your likelihood of having the BRCA1 mutation?

LISA A. CAREY, MD, ScM:

It's a terrific question. There is not an enormous amount of data, because typically the direction of these evaluations is from the mutation to the tumor. However, a couple of small studies have suggested that. And many of us think in the future this will be taken into account, because if you are triple negative, you have a higher likelihood – overall, I think, threefold higher – of having a BRCA1 mutation than if you just take into account things like family history and age. The “however” here is that, regardless, most people with triple-negative breast cancer do not have BRCA1 mutations. But the risk of having one may be a little bit higher, and in my cases, the genetic counselors who are evaluating that risk are nowadays taking that a little more into account as they define the likelihood that someone may carry one of these inherited forms and their recommendations for doing genetic testing.



CALLER:

Thank you.

OPERATOR:

Our next question comes from Wayne, Pennsylvania.

CALLER:

I have a question about metastatic breast cancer treatment. Does the tumor become resistant to the drug or the mechanism? If you've already had a microtubule inhibitor or a DNA repair inhibitor, can you go back on something like that if it's a different drug? Or does your tumor become resistant to that type of inhibitor?

LISA A. CAREY, MD, ScM:

That's a terrific question. It can do both. Sometimes tumors will develop resistance to an overall mechanism of action, and if so, then it doesn't matter if you change from one drug to another within that class. Other times, specific mechanism patterns are effective in one drug within a class and a little bit different in another drug within the class. Many of these drugs have subtle differences.

Unfortunately, we don't have a very good way of telling whether someone is resistant to a mechanism or to an individual drug. But usually, for many of these drugs, there is already information about what proportion of patients will respond to one drug within a class who didn't respond to another one. In fact, for things like, for example, taxanes, there is often a 10 to 15 percent non-cross-resistance – resistance to one drug within the class but not to another, making it reasonable to go back and try those drugs at some point.

CALLER:

Thank you very much.

OPERATOR:

Our next question comes from Saratoga, California.

CALLER:

My question is about my daughter, who is 30 and was diagnosed with breast cancer six years ago, and it's metastasized. It was ER positive originally. She had chemo. But in the metastatic case, the hormone therapy did not work at all. So do you classify somebody like that as a triple negative? Do you have experience with that in terms of drugs to treat that?

LISA A. CAREY, MD, ScM:

There are two answers to that. The question is: In someone who is ER positive but hormone insensitive, does that reflect that the ER-positive assay wasn't accurate and they were a different subtype, or is it insensitivity to hormones through some other mechanism? You can't honestly tell. We often will biopsy people after they develop stage IV or metastatic disease, because in a small percentage, the tumor itself will seem to change those proteins: ER, PR or HER2.

What seemed to be effective in the early setting may not be effective in the later setting, because either the tumor seems to have shifted over time, or the original tests – no test is 100 percent accurate – weren't as good, particularly in older tests, as they are today. However, it's also clear that women who are hormone receptor positive, and if you do subtyping, they fall within an ER positive subtype, can be hormone insensitive. A lot of ongoing studies are trying to sort out hormone insensitivity and the reasons for hormone insensitivity in the setting of a tumor that seems to be driven by hormones.

Now, in an individual class, you cannot, unfortunately, tell which it is. I think getting repeat biopsies in the stage IV setting – when someone is first diagnosed with a relapse, for a variety of reasons, we often will try to get a sample in order to see whether there are some changes in these proteins. But it can happen whether or not the tumor is ER positive.

CALLER:

In that case, then do you go through and treat the person with the same Avastin? ... And if you've gone through Xeloda, Avastin, and now are on taxanes, do you treat it the same way as you would a triple negative?

LISA A. CAREY, MD, ScM:

Since we use conventional agents for all kinds of breast cancers, the tendency for most oncologists, if they have a sense that a tumor has some evidence of hormone responsiveness, is to try to give antiestrogen-type approaches. There are many, many different drugs that do that. If, however, the cancer itself appears not to be behaving as a hormone-sensitive tumor, and targeting that approach doesn't seem to be effective, then we simply go to the other drugs that work in a non-selective way, and those are a variety of chemotherapies and include the antiangiogenic drugs, as I mentioned.

ELYSE S. CAPLAN, MA:

Thank you for your question.

OPERATOR:

Your next question comes from Raleigh, North Carolina.

CALLER:

Hi, Dr. Carey. There doesn't seem to be a whole lot of information about any relationship between pregnancy and triple-negative cancer. Is there anything out there that women that are getting pregnant need to be concerned about?

LISA A. CAREY, MD, ScM:

No, there really isn't a lot of data. Fortunately, development of breast cancer during pregnancy is uncommon, regardless of subtype, so, blessedly, we don't have to encounter this very commonly. They are often hormone receptor positive, so this is really not something that I would say is an association that anybody knows much about at this point.

CALLER:

Thank you.

OPERATOR:

Your next question comes from Madeira, Ohio.

CALLER:

Hi, Doctor. I was wondering, if you have a recurrence and you are three years out, are the drugs as effective as if you have an initial diagnosis? Has this affected our prognosis?

LISA A. CAREY, MD, ScM:

I'm sorry; what kind of recurrence are we talking about?

CALLER:

If you have a recurrence of your cancer – say you are three years out from your initial diagnosis and you went three years without having cancer; you were kind of in remission.

LISA A. CAREY, MD, ScM:

When you say recurrence, you mean in the breast, like a new breast cancer?

CALLER:

No, like an occurrence, a metastasis in the body.

LISA A. CAREY, MD, ScM:

Oh, metastasis?

CALLER:

Yeah.



LISA A. CAREY, MD, ScM:

The difference between the prognosis in early breast cancer and the prognosis in advanced disease – of course, they're very different. Stages I through III are considered curable breast cancer and are clearly curable using conventional methods. And with mortality from breast cancer, there's been a substantial improvement in it. About half of that improvement comes from improved treatments for early breast cancer that help prevent relapse. If relapse happens and it's stage IV – the reason I was trying to get a little more granularity to the question is because recurrence isn't one thing.

Recurrence in a breast after lumpectomy doesn't have any implications for prognosis to any significant degree. It certainly has implications for treatment, but it doesn't carry at all the same kind of implications. Recurrence on a chest wall after a mastectomy does have a little more prognostic significance, but, again, it is still considered curable.

CALLER:

What about recurrence under the arm, in the axilla area?

LISA A. CAREY, MD, ScM:

Again, that's local disease, and aggressive management is required, but – again, not being able to comment about specifics – in general, local disease can be managed with multimodality therapy, and many times – not in all circumstances, but many times – we do that with the intent to try and cure them. That's not the case if it's distant disease like a liver or bone or lung. So it's important to keep those separate. We don't consider liver, lung and bone as being curable, but we do consider them controllable.

CALLER:

Has prognosis gone up with the advent of these new drugs?

LISA A. CAREY, MD, ScM:

Yeah, prognosis improves all the time.

CALLER:

Oh, good.

LISA A. CAREY, MD, ScM:

Thankfully, yes. We certainly have a ways to go, but every report, it looks better than the last one, and that's a really comforting and reassuring thing that we're going in the right direction.

CALLER:

Great. That's great. Thank you so much.

OPERATOR:

Your next question comes from Hanover, New Hampshire.

CALLER:

I've read a lot recently about different lifestyle modifications people can try to do to prevent the recurrence of their breast cancer – things like diet or exercise or alcohol. To what degree do we know whether or not these things benefit triple-negative breast cancer or if there's specific advice for people who have already been through early-stage treatments on what they can do to help improve their chances of preventing a recurrence?

LISA A. CAREY, MD, ScM:

At this point, this is an incredibly exciting area for the future. We know that there are data that suggest that some things you can do, like diet, exercise and alcohol, certainly don't hurt the likelihood of it coming back and may, in fact, help it, but it's not clear. And whether it helps one subtype more than another – there's a hint that some of these risk factors are stronger than others in particular subtypes of cancer, but it's not clear yet.

Many of us tell our patients that a low-fat diet, active lifestyle and control of the other kinds of sort of healthy-life things can only be good from a general sense, but we can't really say the extent to which modifying the diet, in an American woman, can affect her likelihood of relapse. I think most of us think of it primarily in that it may help and it's unlikely to hurt, and more data will be coming to help guide us.

OPERATOR:

Our next question comes from Denver, Colorado.

CALLER:

I wanted to follow up on that last question. A couple of years ago, there were some small studies that showed a low-fat diet of about 15 to 20 decreased the rate of recurrence specifically for triple negative. But I know that there were maybe 30 people, a very small sample. I've been trying to maintain that kind of diet, which is a little challenging. How seriously should one take this information?

LISA A. CAREY, MD, ScM:

It's a suggestion, and we really don't know. Again, none of these trials are currently what we call practice-changing or definitive. In many cases, they're a wonderful direction. As you probably

know, several of the interventional studies have not been as encouraging, but, again, when they were set up ten years ago, none of them were set up to try to do this within particular groups. They weren't looking at subtype-specific things, so none of them were set up to answer the question definitively. I think if it's possible to keep to a low-fat diet, it's a very reasonable thing to do.

One of the things I say to my patients is, I think, very important, particularly for metastatic patients. Once a patient of mine develops stage IV disease or even earlier than that, they hear from a lot of people about all the things they should be doing to keep their cancer from coming back. While I think many of these kinds of general good-health approaches – and thankfully, the things that appear to possibly be related to outcome are also the things that are related to good health in general – we don't have anything saying, like, eating hamburgers every day helps your breast cancer or hurts your heart, so you choose. None of that has happened. Everything seems to be in general concordant that healthy lifestyles and healthy diet seems to help a lot of diseases, including cancer, but nothing is definitive.

The caution that I have is that my patients are not responsible for whether or not their cancer comes back. I'm very concerned by the preconceived notion that a patient's behavior is somehow going to affect what the cancer does, and that if the cancer does come back it's somehow her fault. There are simply no data supporting that.

So that's my caveat. I think the healthy lifestyle is a very reasonable thing to do. It may help with outcomes, but it may not. We really don't have enough information about it, in particular, if you start looking at subtypes. But I absolutely have a very serious issue to take with those who say that if a patient isn't doing these things, then she's responsible for her cancer coming back. There's simply no evidence for that. Do you see what I mean?

CALLER:

Yes. Thank you very much.

ELYSE S. CAPLAN, MA:

I thank you for highlighting that, Dr. Carey, because that's another issue that we tend to hear about in women whose breast cancer does return. They're looking at all of the things they did right, and it still happened. So I appreciate you highlighting your viewpoint on that.



OPERATOR:

Our next question comes from New York, New York.

CALLER:

Dr. Carey, I wonder if you can explain what, in the pathology report, “aneuploid DNA” and “Ki-67 staining” mean. I wasn’t able to find any information that a layperson could understand anywhere.

LISA A. CAREY, MD, ScM:

I’m sure.

CALLER:

But it is associated with adverse prognosis.

LISA A. CAREY, MD, ScM:

Yeah. Aneuploidy has to do with whether the cell seems to have the correct – oh, boy, let me summarize. I’ll put them together by saying they’re typically associated with higher-grade cancers. Ki-67 is actually a measure of the proliferation of the tumor, and ploidy has to do with how many copies of genes or chromosomes are in a cell, and whether there seems to be control over the division of the cell’s DNA, the portions that kind of run the cell. If you take them together, aneuploidy goes along with the cell sort of losing control over its own growth and proliferation, and the same is true of Ki-67 being high.

The reason they’re not treated as their own factor is that those characteristics often go along with other characteristics. For example, the triple-negative subtype is more likely to have a higher fraction of the cells that are growing and more abnormalities in the growth and proliferation – what you use to measure it as a characteristic of the tumor. That’s the reason they tend to be grade 3.

CALLER:

Thank you very much.

OPERATOR:

Your next question comes from San Diego, California.

CALLER:

Hi, Dr. Carey, I have a question regarding the taxane drugs. I’ve heard on numerous occasions that there is not a lot of research supporting the taxanes as a second tier in early-stage triple negative.

LISA A. CAREY, MD, ScM:

I don’t know what “second tier” means. There have been thousands of women treated on adjuvant, meaning early breast cancer, taxane trials, and they improve the outcome. They improve the

outcome in all groups to some degree, and in ER negative subgroups even more so than in ER positive subgroups, to the extent that we can measure that. Some studies see less compelling evidence that there’s a difference between different kinds of cancer, but there is a general similarity, particularly if you start adding them all together, that taxanes added to other chemotherapy drugs are effective in this subtype, as in others.

Whether you can use them by themselves, I think, is a separate question, and that’s being studied in a trial called CALGB 40101 [<http://www.cancer.gov/clinicaltrials/CALGB-40101>], which is a straight-up comparison in relatively low-risk patients of AC, which is an old-fashioned anthracycline- or doxorubicin-containing regimen, versus Taxol by itself. The results of that won’t be ready for several years, but it’s a reasonable question. These drugs, I think, do have a role to play, particularly within certain risk categories, added to other chemotherapy. I assume that’s what you mean by second tier, meaning added to other chemotherapy drugs.

CALLER:

Yes, after AC.

LISA A. CAREY, MD, ScM:

Yeah, after AC. I personally don’t have any question that these drugs play a role in any kind of breast cancer if it has a high enough risk that you’re giving more aggressive chemotherapy regimens, but there are also less toxic regimens. Many people are familiar with the regimen TC, which avoids [Adriamycin], or doxorubicin, and instead includes the drug Taxotere, or docetaxel, and that’s quite an effective regimen for even lower-risk patients.

CALLER:

Thank you.

OPERATOR:

Your next question comes from Pottstown, Pennsylvania.

CALLER:

Hi, I have a question about the aggression rate. I was diagnosed with stage I cancer, small tumor, but the aggression was a stage III. Then chemo was recommended, which I chose to have, because I felt that if I didn’t take everything available, then I might regret that decision later. It was difficult, because I had a choice. Mainly I’m concerned about medication, that we don’t feel that we’re in the same group of people who are eligible for

medication if you are not ER and PR negative and HER2 negative. My support group people who are in my same category say, “Wow, we’re out there in la-la land, and no one is allowing us anything.” I think that is our main concern, and my concern is whether any medication is available to prevent a relapse.

LISA A. CAREY, MD, ScM:

I was saying earlier that conventional chemotherapy actually is quite effective in this, and what there isn’t knowledge of a targeted, or biologic, agent that helps prevent relapse. But chemo is effective and ought to be used when appropriate.

CALLER:

I did have the chemo. However, I think the other women in my same group are saying, “Wow, now we have nothing else to do.” It’s sort of like, “Okay, now we finished our treatment, and everyone says goodbye; we’ll see you in six months.”

LISA A. CAREY, MD, ScM:

That happens with all groups of patients. It’s just that some of the targeted agents happen to be pills that we give over a long time. But, as I mentioned, there may be a benefit to that in the sense that the relapse rate is higher early for this subtype, and chemotherapy works more effectively early. There is less of a risk as you get to be ten years out than there is in somebody who’s taking pills ten years out, if you see what I mean. So that may not be necessarily a bad thing.

CALLER:

I’m just one year after my treatment.

ELYSE S. CAPLAN, MA:

I think what you and some of the members of your group are talking about is very common . . . and I think Dr. Carey has highlighted nicely how chemotherapy is the single most effective treatment that we know of today for triple-negative breast cancer – and holding on to that hope, as Dr. Carey outlined some interesting research approaches that are being tested that hopefully will improve treatment and outcomes for women with triple-negative breast cancer. Thanks so much for your question; we’re going to move on to the next one.

LISA A. CAREY, MD, ScM:

Elyse, let me add something parenthetical about this. It has nothing to do with the subtype, but for those patients who go through adjuvant therapy and surgery and radiation and chemo, there is a tendency after finishing very active care –



whether or not they're receiving antiestrogen pills, those who finish their infusion of Herceptin, those who finish their radiation, at the point where there's less active management of the cancer, it's a very psychologically hard time.

Women who feel sort of anxious or depressed or frightened, that is – it's funny, because many of my patients would say, I thought, "Wow, okay, I'm done. I should be celebrating. And instead I just feel incredibly anxious." That is normal, and they shouldn't think they're going crazy. It is very normal to have that feeling. If you need help managing that – it's a very anxiety-provoking time – seek some help. This is not something that is easy for anybody.

ELYSE S. CAPLAN, MA:

I think that's a great point, and I appreciate you bringing that up. The survivorship issues of transitioning from active treatment into follow-up definitely can feel like a precarious time.

LISA A. CAREY, MD, ScM:

Very much so, and I think there is less outside support. They're now six months after their diagnosis or a year after their diagnosis, so there are fewer casseroles being dropped off.

ELYSE S. CAPLAN, MA:

That's a good point.

OPERATOR:

Your next question comes from Edmond, Oklahoma.

CALLER:

I want to follow up on the chemotherapy question. Is there any evidence that the way chemotherapy is given works any different or any better, such as dose dense or dose escalation?

LISA A. CAREY, MD, ScM:

Dose-dense therapy, which means that the same drug is being given more frequently, has been shown, with a particular regimen, to be effective – specifically the dose-dense approach to AC – or Adriamycin, also known as doxorubicin, and cyclophosphamide, or Cytosan – followed by Taxol, or paclitaxel. The old-fashioned way of giving it from a few years ago was once every three weeks. There was a study where they gave the same drugs at the same doses, but instead of every three weeks they gave them every two weeks. They were more effective given every two weeks.

That's not necessarily true of all drugs, and, in fact, there seems to be probably less dependence on timing for other taxanes. Taxotere, or docetaxel, may have less of an impact by changing from less

frequent to more frequent dosing. The approach of altering schedule – there's a reason that may work in some drugs, but there's also a reason it may not work in all drugs. It's sort of a theoretical construct that comes from laboratory studies and mathematical models of how cells grow and how chemotherapy works.

The shorter answer is that I think it's correct to use dose-dense approaches when there is a proven dose-dense approach. AC-T is a classic example where it's a proven dose-dense approach. Other approaches are being studied, like what some people call the metronomic dosing, which is weekly at lower doses. That's being studied in clinical trials, and I wouldn't do it off of a clinical trial – I wouldn't use a dose-dense approach to drugs that haven't been studied in that way.

CALLER:

But we don't know whether there's a difference in how dose-dense works for the basal-like subtype, is that correct?

LISA A. CAREY, MD, ScM:

That is correct.

CALLER:

What about dose escalation? Peripheral stem cell transplants – I know that's not really being done anymore, but is there any thought that that could have been part of the reason why it worked in some women and not in others?

LISA A. CAREY, MD, ScM:

There is some thought, and there are some conflicting results when they go back and do re-analyses or meta-analyses. I think the jury is still out on that. It's a very reasonable thought. Unless there is a compelling reason to do so, I don't think anybody is going to go back to the days of high-dose chemotherapy. This is something they would have to have a lot more evidence for, and, in truth, the evidence that is there is conflicting on this topic.

CALLER:

Thanks.

OPERATOR:

Our next question comes from Tonawanda, New York.

CALLER:

I was diagnosed with stage III breast cancer on the left side, and it has recently recurred in the lymph nodes under the right arm. I was wondering if that is considered curable.

LISA A. CAREY, MD, ScM:

The general question has to do with contralateral, or on the other side, development of lymph nodes. I think it's not clear. If cancers are on one side and then three years later or two years later or whenever, the lymph nodes contain cancer on the other side, and we can't see it any place else, we always have a very high suspicion that it may be in that other breast. There are some cancers that are incredibly small in the breast and got into the lymph nodes, so we typically approach it as if it's coming from that other breast, and we manage it the same way. Now, if it's in those other lymph nodes and also in other sites of the body, then we think of it as metastatic. But if it's just in those lymph nodes, then we do a pretty exhaustive search for something in the breast and tend to manage it similarly.

CALLER:

Would it be considered the same cancer that has metastasized, or would it be a new primary?

LISA A. CAREY, MD, ScM:

That's what that search has to determine. In the end of the day, someone has to make that call. Not knowing the specifics, I couldn't do it for this case.

CALLER:

I understand. Just quickly, when the breast cancer started three years ago, it was very high estrogen positive, and now it went to HER2 positive, and now it's triple negative. Is that uncommon for it to change pathways that frequently?

LISA A. CAREY, MD, ScM:

A small proportion of the time, cancers, as they progress, will change their receptor types. It's a little unusual for a tumor to completely change its appearance, completely change its proteins, and that would be one of the markers that we would use as we were trying to decide whether something was a new cancer versus an old cancer recurring.

CALLER:

I see.

LISA A. CAREY, MD, ScM:

With a completely different receptor picture suggesting a new cancer, as opposed to an old one come back.

CALLER:

Thank you.



OPERATOR:

Your next question comes from Miami, Florida.

CALLER:

After the initial treatment, Dr. Carey, of chemo – and in this case it was Cytoxan, epirubicin and 5-FU – and a cycle of radiation, are there tests that should be done at that point on the patient in order to see if anything comes up? Or is that pretty much the treatment without any follow-up tests until, I don't know, a follow-up of three months with your oncologist?

LISA A. CAREY, MD, ScM:

That's a great question. It's something that many patients ask. This is assuming this is early breast cancer, where they're given chemotherapy and radiation and an approach combined with surgery, trying to move them to being without any cancer, cancer-free. Then we follow them really clinically, meaning physical exam and a history, every few months for a few years and then at decreasing frequencies as a person gets out from their diagnosis. There are no tests that really help us improve outcome. For example, patients will ask us, "I heard about fancy new PET scans and all sorts of things, and does this help find my cancer earlier and help me potentially live longer if my cancer comes back? Or are there blood tests?"

The short answer is that there aren't any blood tests or scans, outside of mammography and studies directed at the breast for finding either the cancer come back in the breast or a new cancer – there aren't any that help otherwise. There are some tests that can be done that may be positive and sometimes may pick up a cancer before it becomes more clinically evident. But that doesn't necessarily help a person live longer; that's why we don't do them. In fact, we have national guidelines about this, and they do not support blood tests or routine scanning outside of evaluations of the breast.

CALLER:

Thank you very much.

OPERATOR:

Our next question comes from Washington, D.C.

CALLER:

Hello. I have a question related to one I think you already answered from the woman in Colorado regarding the "Dietary Fat Reduction and Breast Cancer Outcome" study that was published in the *Journal of the National*

Cancer Institute in December of 2006 [<http://www.cancer.gov/clinicaltrials/results/low-fat-diet0505>]. That study concluded that reducing dietary fat intake may improve relapse-free survival. But in the study itself, they didn't control for a number of factors – for instance, weight change or, in general, the Body Mass Index of the individual and the dietary factors other than fat intake. I wondered, because I've been advised to be following this extremely low-fat diet, which I agree is extremely challenging, if you think there may be some other factors besides just fat intake that may be at –

LISA A. CAREY, MD, ScM:

I assume you're talking about the WIN[S— Women's Intervention Nutrition] study. This was a really nicely done study. However, the caveats to it – there are a couple of them. One is that it's one study, and there is always a play of chance whenever there is one study result, particularly if there are not a lot of others – the evidence is not as supportive elsewhere. The second part is that, as you say, there were a lot of things that they couldn't control. They could control the dietary fat, and they did.

I think one of the really remarkable things in this study, which was a very intensive interventional study, was that the patients not only reduced their fat intake, but it was maintained over time, which is really, really hard to do. But they tried not to have people lose weight. They tried to control for many of the other things, but in truth, people did lose a few pounds in the intervention compared with the control, and that may have played a role. It may be not that they ate less fat; it may be that they ate more of something else. So exactly what happened in there is a little bit harder to tease out.

That study is among the reasons why we say this is a reasonable thing, to try to do what you can do to have a healthy lifestyle, but my caveat was to not beat yourself up if you're having a hard time doing that. We do not know exactly the extent to which this will impact an individual person's recurrence risk.

CALLER:

Thank you.

OPERATOR:

Your next question comes from Knoxville, Tennessee.

CALLER:

Yes, you all brought up the fact about the BRCA1 gene. What about the BRCA2 gene, if you're positive for it and getting triple negative?

LISA A. CAREY, MD, ScM:

There is a little less information. Usually people who carry BRCA2 mutations don't get triple-negative or basal-like breast cancer, so that's a little bit harder to tease out. There aren't enough of them for us to say anything particularly relevant, except insofar as BRCA2 also has implications similar to BRCA1 in terms of DNA repair pathways. What holds true for BRCA1, in terms of it turning out that the ability to damage DNA in triple-negative breast cancer with or without BRCA1 mutations holds true, it will probably – although not definitively so – also hold true for BRCA2. Those two things have some relationship, but BRCA2 mutation carriers, when they get breast cancer, usually get ER positive breast cancers.

CALLER:

I carry that gene – my daughter and I both – and I have the triple negative. I'm the first person I found that has the BRCA2 and the triple-negative cancer.

LISA A. CAREY, MD, ScM:

Exactly. It's uncommon.

CALLER:

Okay, thank you.

OPERATOR:

Our next question comes from Wynnewood, Pennsylvania.

CALLER:

Hello. I have a two-pronged question. I know that with the ER positive patients, there have been reports of people who have had survival rates with metastatic cancer ten years, 12 years out. Has there been any similar longevity with the triple negatives?

LISA A. CAREY, MD, ScM:

Not so much. It's a little bit harder to tease out than the ER positive ones. There's an enormous variability in breast cancers, whether or not your breast cancer is hormone receptor positive or hormone receptor negative. Some people, hormone receptor positive and regardless, simply don't do very well, and they don't respond to any of the therapies that are given. Others look the same to us, and their disease is well controlled with the drugs that we have for many, many years. In my personal experience, the same thing is true of hormone receptor-negative breast cancer.

CALLER:

Or triple negative specifically.



LISA A. CAREY, MD, ScM:

Again, once you start getting into subtypes of subtypes, there's even less information that can help you. The triple-negative group – again, early relapses have a tendency to carry a poorer prognosis than later relapses, so sometimes that gives us a hint. But there is just so much variability.

In my clinic, someone will say, what's the average? I'll say, okay, we have averages for all sorts of things. But let me tell you why averages in this particular circumstance are not very helpful. If I tell you that you were going to go to a picnic, and at the picnic the average age would be 50, that may be totally true; however, some of the people at the picnic are babies, and some of the people at the picnic are nonagenarians. For individual people there, the number 50 is irrelevant. That's the case for breast cancer in general. We can come up with prognostic estimates, but even when we get more sophisticated about these things, it may not be meaningful.

CALLER:

I see. My other question is how easy is it, or can they ever actually determine which breast cancer metastasized, if there was one 14 years ago and another two years ago – both small, but node negative, and there is metastasis two years after the second diagnosis? Can they determine which one metastasized, or does it even make a difference?

LISA A. CAREY, MD, ScM:

In a person who has two breast cancers, whether they're at the same time or at different times, and then develops metastatic disease, the focus usually is on whether or not the cancer, once it's come back, has targetable differences – whether it matters in terms of treatments you might choose. For example, if a woman has one breast cancer that's HER2 positive, and then has another breast cancer two years later that's HER2 negative, it's very important to know what the metastasis came from, because it's going to make a big difference in terms of what treatments you choose. Same thing for hormone receptor positive and hormone receptor negative. If the two cancers look more or less the same from the standpoint of targetable differences, then it's a little less important.

CALLER:

All right, thank you very much.

OPERATOR:

Your next question comes from Georgetown, Texas.

CALLER:

My question is if you're triple negative on one side, you're diagnosed with breast cancer, and you're in remission, if you get a totally separate cancer on the other side, is it automatically triple-negative also? Or could it be receptor positive?

LISA A. CAREY, MD, ScM:

No, it can be receptor positive.

CALLER:

So it can go either way if you get it on the other side?

LISA A. CAREY, MD, ScM:

Yes.

CALLER:

Okay, thank you.

OPERATOR:

Your next question comes from Chicago, Illinois.

CALLER:

Hi, Dr. Carey. Thank you for taking my call, all of our calls, actually.

LISA A. CAREY, MD, ScM:

My pleasure.

CALLER:

I'm still reeling from BRCA2 and triple negative, because I just found that out. But my question is, a complete pathological response to either neoadjuvant or adjuvant chemo, do you recommend radiation for triple negative?

LISA A. CAREY, MD, ScM:

Radiation indications are the same for all the subtypes of breast cancer.

CALLER:

All? All? Okay.

LISA A. CAREY, MD, ScM:

It's definitely anatomically driven.

CALLER:

All right, I appreciate it. Thank you very much.

OPERATOR:

Your next question comes from Beaverton, Oregon.

CALLER:

I am also BRCA2, ER/PR negative, and I developed my cancer way, way beyond menopause. At this point, can I assume that the cancer may not even be related to BRCA2? Or is that a faulty assumption?

LISA A. CAREY, MD, ScM:

I think any breast cancer that develops in the setting of BRCA1 or 2, it's certainly reasonable to assume that the BRCA1 or 2 mutation played a role in its development. But you're right – it's possible that some of them were going to develop regardless.

CALLER:

The other question I want to ask: I was node negative, but I had angiolymphatic invasion – I don't know how much; they didn't state that. Does that have any relation to the prognosis?

LISA A. CAREY, MD, ScM:

That's somewhat debated, but it's certainly associated with a poorer prognosis. How much that happens without the nodal involvement – usually lymphovascular invasion and nodal involvement tend to go together, but not always, and how much it independently contributes to prognosis is a little bit uncertain, although many people think it contributes some. It's not as well studied, unfortunately.

CALLER:

Thank you.

OPERATOR:

Your next question comes from Durham, North Carolina.

CALLER:

I got to thinking about triple-negative and other cancers – breast cancers in men, for example, or melanoma or whatever. I'm wondering if perhaps the EGFR that I think you talked about, the HER1 through HER4, were maybe signaling each other and causing the cancer to grow, if there was some way to interfere with those others. As near as I can tell, it would be on all the cells, whether you're male or female.



LISA A. CAREY, MD, ScM:

We talked about HER2, which is the one that has a known role to play in breast cancer, and HER1, which has a potential role in this particular subtype of breast cancer. As you mentioned, there are two other family members, HER3 and HER4, and these receptors can sometimes behave by themselves in the case of HER2, when it's overexpressed. Or, more commonly, they can operate in concert, and they attach to one another in what are called heterodimers. How the relative expression of all four family members may play a role in cell growth is a very interesting concept and one that a number of very specialized labs are looking at, so we'll hopefully have a little more information for you as we go along.

CALLER:

But blocking all four of them wouldn't offer an advantage that we know of at this time?

LISA A. CAREY, MD, ScM:

No.

ELYSE S. CAPLAN, MA:

Thank you. I see that our 90 minutes is speeding by so quickly. On behalf of Living Beyond Breast Cancer and the Triple Negative Breast Cancer Foundation, I'd love to thank Dr. Carey for her time and expertise and excellent information. I also want to thank all the participants. The questions each time we do a teleconference are wonderful. This is a knowledgeable, informed audience. We appreciate the research you've done in trying to get clarity so that you can go back and get the kind of health care you need and you have fewer questions and more information. We know more information translates into you feeling in much better control of your disease.

To Dr. Carey's point earlier about the survivorship concerns, which we hear about, and that's what we're here to help women with, there are several resources I'd like to call out. Number one, Living Beyond Breast Cancer's toll-free Survivors' Helpline. We have women who would be happy to talk to you, if you have any concerns about post-treatment, getting back on track and dealing with moving into recovery. That toll-free number is (888) 753-LBBC [5222]. Again, we have trained volunteers who are breast cancer survivors who are happy to offer peer emotional support.

The Triple Negative Breast Cancer Foundation also has some very active discussion forums, and you can find them at tnbcfoundation.org [<http://tnbcfoundation.org/index.html>]. Perhaps for those of you who like to connect online, that would be a nice way for you to get some support around some of your concerns. Dr. Carey, do you have any closing remarks you'd like to offer?

LISA A. CAREY, MD, ScM:

I very much appreciate how attentively people clearly were listening, and thank you for your time. I hope this was informative to everyone, and if it wasn't, and if there was some way in which it wasn't, please let us know.

ELYSE S. CAPLAN, MA:

Absolutely. Just to close, we do appreciate the generous support of Susan G. Komen for the Cure, which did help to make today's program possible. Thanks, everyone.

[END OF TRANSCRIPT]