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## Medical Update for Young Women

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Eric P. Winer, MD

### ERIC P. WINER, MD:

Whoa; those lights are bright. Before I get to my topic, let me just talk for a few minutes. I thought it was going to be a very relaxing talk. Then I walked in last night and ran into Marcia [Stein, CEO of the Young Survival Coalition; <http://www.youngsurvival.org>]. . . . The minute you realize you're lecturing or talking to people you know, the stakes go up. (Laughter)

Later, one of you out there recognized me in the elevator and said, "Are you Dr. Winer? I came here to see you." And I thought, "Oh my God. I hope there are lots of other good reasons for you to have come." The pressure was starting to build. (Laughter)

In any case, I hope to be able to pass on some useful information to all of you.

I don't entirely know why I became a breast cancer doctor. I have some guesses. When I was 18 or 19, one of my uncle's many [former] wives—my favorite of those wives (laughter)—developed breast cancer. A couple of years later she died from breast cancer. For whatever reasons, even though I wasn't in contact with her at the time, it had a pretty significant impact on me.

When I was in medical school I did my thesis on breast cancer, not really thinking that I'd become a breast cancer doctor. But somehow I was drawn to it. Throughout training I'd thought about doing all sorts of things: I thought about being a psychiatrist; I thought about being a cardiologist. In truth, before that, I had thought about being a Russian historian. But, in the end, I found that oncology, taking care of patients with cancer and doing research related to cancer more compelling than anything else. About 20 years ago, when I was at Duke as a fellow, there was a spot for the breast cancer doctor. This was a long time ago; it was before there was so much sub-specialization. And, as a second-year fellow 21 years ago, I became the breast cancer expert at Duke—something I still can't quite believe.

I love what I do. I think I've been able to bring a little bit to the field. And it certainly has never ceased to provide me pleasure to see a new patient and to be able to help that person, and to be able to work with my colleagues and try to push the field forward—because, although you will hear that there have been some advances and that our medical care is far more advanced than it was in 1988, when I was that second-year fellow, the truth is that there are still 40,000 women in the United States who die from breast cancer each year. There are still [approximately] 400,000 women worldwide who die from breast cancer each year. That really needs to change sometime soon—hopefully in the next decade or sooner . . . I think that we have the tools to begin to really make a difference over these next few years. But we have to do so with a lot of very thoughtful research.

I think that the single biggest change in the way we deal with breast cancer, or take care of patients with breast cancer, over the course of the last five to ten years is that we now fully embrace the fact that breast cancer is not one disease. On some level, we always knew this. But it was something that wasn't fully appreciated. And, more importantly, it was not something that we thought about in the clinic each and every day.

We've learned the importance of hormonal therapy in women with estrogen receptor-positive breast cancer. We've recently had some data . . . on the use of bisphosphonates in young women with breast cancer. For women who have HER2 positive breast cancer . . . we have a whole host of new agents—that's, perhaps, the single area in which we've made huge progress over the course of the past five years. And, finally, in the setting of what's often called triple-negative breast cancer, or breast cancer that is estrogen and progesterone receptor negative and HER2 negative, we've made some limited advances, but we need to do a lot of work.

How common is breast cancer in young women? Many of you are familiar with this. This is data from the SEER [Surveillance, Epidemiology and End Results] program [<http://seer.cancer.gov>]. Of all cases of breast cancer in the United States, only 6 percent involve women under the age of 40. But that still means that there are 11,000 women under the age of 40 who are diagnosed with breast cancer each and every year, making it a far more common malignancy . . . than many of the other cancers that arise in men and women in the United States. If we broaden our definition of young, as some of you might like to do—and certainly many elsewhere would like to do—and say that "young" pertains to women who are, perhaps, under 45 or under 50, you can see that the numbers increase substantially.

In developing countries, the proportion of young women who have breast cancer appears to be somewhat higher. It's probably not because breast cancer in young women is so much more common there, but because, in developing countries, women aren't living as long, and we therefore don't see the breast cancer that arises in older women.

I mentioned before that we used to think of breast cancer as one entity; as a monolithic force. What has changed is that we now think of it as very different diseases. This is my colleague's son's drawing of breast cancer. He's pretty good at looking through a microscope and drawing what he sees on paper. If you looked at these cancers under the microscope—I realize that many of you don't have training to do this, but you can look at those four different pictures—you'd say, "They look like four very different entities." And they are. These are all invasive breast cancers, but they look very different from one another. The picture on the lower right-hand corner of your screen is of a very small tubular cancer; a cancer that, if it hadn't been diagnosed, might never have bothered that woman



and is almost certainly not ever going to threaten that woman's life. If you look at the picture in the other corner, you see a much higher grade cancer; one that could be much more concerning.

For years clinicians have known that breast cancer isn't one disease; that it's a highly variable disease. But what has changed in the last five years is that, through a careful analysis of clinical data from clinical trials over the course of the last two decades, as well as from the explosion in so-called genomics, we now think of breast cancer as four pretty distinct entities. There is triple-negative breast cancer. There's HER2 positive breast cancer. And then there are the largest groups of tumors that affect women, even young women: estrogen receptor-positive and HER2 negative cancers. If we look at women of all ages, estrogen receptor-positive and HER2 negative breast cancers account for about 70 percent of all breast cancer. If we look at younger women, it's probably more like 50 percent. But this is a very, very heterogeneous group. For some of these women, hormonal therapy is absolutely the most important therapy—it's perhaps the only therapy, apart from surgery or radiation—that they should receive. For others, treatments such as chemotherapy remain very important.

This is something that is very frequently shown in breast cancer lectures these days. This is a map of genes from different breast tumors. If you go across the top, each of those lines represents an individual breast tumor. If you go down, you can see, listed on the right-hand portion of the slide, all these different genes. For reasons that don't make sense to me, because I think of green as "go" and red as "stop," in this case red means that a gene is turned on and green means that a gene is turned off. We're now able to sort of profile breast tumors for research purposes, and we can see the different patterns that emerge.

You can see that there are certain groups of tumors—take the ones on the far left side, for example—where, down at the bottom, there's a lot of green. Those genes are turned off. In other areas, there's much more red. The tumors shown on the far left portion of the slide are triple-negative tumors. Those red genes, next to E, that are turned on are all genes that are very commonly expressed in triple-negative tumors. In contrast, the tumors shown in the next area are HER2 positive tumors. The red genes at the top are genes that are very frequently associated with HER2 positive breast cancer.

This is important, not just because it [gives us a way to] sort the genes, but also because, if we look at women who were treated with chemotherapy only, we can see that these different groups of patients have very, very different outcomes. Some of them do much better than others. Some of them do much worse. Now, these aren't real patients here. This is a hypothetical clinical trial. In a clinical trial we often compare treatment A to treatment B, and sometimes to treatments C, D and E as well. Wouldn't it be great if every clinical trial we did showed this kind of difference? You might say that this looks like a small difference to you, but in many of the clinical trials we do we see 3, 5 or 10 percent improvement—so a 25 percent improvement would really be a big deal.

Let's imagine we're comparing treatments A and B and that we include all women with breast cancer. Let's imagine we include everyone in this room in that clinical trial. Say we find that there's a 25 percent improvement in outcome, and say we conclude that, for each and every one of you, getting the new treatment—treatment A—is the right approach. Let's imagine that treatment A is a new drug that is very expensive and that it has a reasonable number of side effects. Is it right to conclude that we should just give all of you that drug?

Well, if we begin to think of breast cancer as not one disease, but as a family of diseases, it's possible that [this 25-percent improvement may be achieved] in a few different ways. If you look at the top right side, you can see that [this is] one way that [works] for every single subtype of breast cancer, that in fact there is that same difference, that this is a treatment that is broadly applicable to all women with breast cancer. Everybody should take it. Everybody gets a 25-percent benefit. In contrast, you can see, on the bottom, that there are other ways that you can get to that 25-percent improvement. And those ways include the possibility that for some women there's a huge benefit, that in fact the treatment is entirely curative for some and without it all women do poorly. But for others, there's actually a worsening of the outcome.

That's probably not how it really is most of the time. But, in fact, when we used to lump all patients together and do a single clinical trial and conclude that there was a 4-percent benefit or a 3-percent benefit or a 10-percent benefit, what we missed in those generalizations was the fact that

there were probably some patients who had an absolutely enormous benefit, and others who got virtually nothing out of the treatment. Understanding that is absolutely critical, and that's where we have begun to make some progress.

Let's talk about hormonal therapy for estrogen receptor-positive and progesterone receptor-positive cancer. Every once in a while, someone will say, "My tumor was estrogen receptor negative but it was progesterone receptor positive. What does that mean?" That happens about 3 percent of the time. That is a cancer that is considered to be hormonally sensitive. Frequently, that negative estrogen receptor is a false negative.

We know that, with women who have estrogen receptor-positive breast cancer and who are premenopausal—as is the case, of course, with almost all young women—there are a number of different treatments that can be considered. Those treatments include tamoxifen; ovarian suppression, or oophorectomy, which is removal of the ovaries; and, occasionally, aromatase inhibitors. These are drugs that are used primarily in postmenopausal women. In order to give them, we have to suppress a woman's ovaries. In my view, these should not be considered a standard treatment for young women with breast cancer. And ... we're learning more and more that not all women need to receive chemotherapy.

In 2009 the absolute standard treatment for a woman who is premenopausal and who has estrogen receptor-positive breast cancer remains tamoxifen, administered for a period of five years. We know that, looking at women across the board—looking at all premenopausal women with estrogen receptor-positive breast cancer—a five-year course of tamoxifen prevents recurrences in about half of all women who would have had a recurrence. That's a big benefit.

What about the role of ovarian suppression or removal of the ovaries? This gets discussed a great deal. How many of you have had conversations with your doctors about whether or not something should be done in terms of your ovaries—either turning off their function or removing them? [I see] lots and lots of hands, so this, presumably, is something that you're familiar with.

I want to take this opportunity to make a very important point. If I say something that [contradicts or conflicts] with what your doctor has told you, that doesn't mean your doctor is wrong. I can't possibly be familiar with all the



aspects of your situation. Also, there are times when people disagree, of course, and there are legitimate disagreements. But there are also times when there are nuances in someone's case that makes someone recommend one treatment versus another. I can see that some people have ovarian suppression because there are a lot of people waving fans, as if they have hot flashes. (Laughter) In any case, I think it's really important to know that you can't come to a lecture and walk away from it thinking that something you're doing is wrong. It is conceivable that you might listen to a lecture and then say, "I'm going to ask my doctor about that. I'm going to get another opinion." But not for a minute do I want you to lose confidence in something that you have heard from the people who are directly taking care of you.

Let's talk about ovarian suppression and all of the controversies. This is from the Oxford Overview, a group of investigators, which I'm pleased to be part of, who have pooled data from across the world. [Editor's Note: The Oxford Overview, in Oxford, England, analyzes the data of studies conducted by the Early Breast Cancer Trials Collaborative Group.] Sometimes we're criticized for not collaborating enough. [In reality,] this is the ultimate collaboration. [The group has attempted] to look at the benefits of ovarian suppression in women with estrogen receptor-positive breast cancer.

You can see, because there's space between the curves, that there is a reduction in the risk that a woman will have a recurrence and an improvement in mortality or survival associated with the use of ovarian suppression. What's important here is that this result was seen in women for whom ovarian suppression was the only treatment given. So, if you don't have chemotherapy or drugs like tamoxifen available to you and you're a premenopausal woman who has estrogen receptor-positive breast cancer, there's no question that you should suppress the functioning of your ovaries rather than do no treatment. But how does this fit in when we use it in an additive fashion; when we give it in addition to tamoxifen or in addition to chemotherapy?

There have been a number of different trials. The problem is that none of the trials is quite what we want. Most of them were done in Europe. There's nothing wrong with European trials, but the European trials, for a number of years, were designed a little differently from the types of trials that would have been done in the United States

and that would have answered some of the questions we had. Most of the European trials asked whether or not [results obtained via] chemotherapy [are equivalent to those obtained via] ovarian suppression; [some looked at chemotherapy versus] ovarian suppression plus tamoxifen. They all concluded that, in women with estrogen receptor-positive breast cancer, ovarian suppression, either with tamoxifen or, in some cases, without it, seemed to be about as good as a course of CMF-like chemotherapy. This was useful information, but it didn't give us quite what we needed.

A trial conducted in the United States gave us more information, but it didn't quite fill the gaps [<http://www.ncbi.nlm.nih.gov/pubmed/16087950?dopt=Abstract>]. This trial was led by Nancy Davidson, who was at Hopkins for many years and who recently moved to the University of Pittsburgh to direct its cancer center [University of Pittsburgh Cancer Institute; <http://upci.upmc.edu/>]. The trial looked at chemotherapy alone, chemotherapy plus ovarian suppression—that's what goserelin is—and chemotherapy plus goserelin plus tamoxifen. Now, you might ask why tamoxifen wasn't in all of the treatment arms, given that five years of tamoxifen is the standard treatment. The problem is that this study was started over 15 years ago, when tamoxifen wasn't known to be the standard treatment. This is illustrative of a situation that comes up time and time again—we have clinical trials that were started at a time when there was one standard of care, but over the course of time the standard of care has evolved, and we have to figure out how to fit that trial in with our current practice.

At any rate, what did the study show? Well, if we look at the group as a whole—these are all premenopausal women with estrogen receptor-positive breast cancer—you can see that there is a benefit when you add tamoxifen—that is the green line—but that the two other curves, the blue and the black, are essentially superimposable, and there seems to be very little benefit to just adding ovarian suppression to chemotherapy.

But there's a big problem here: many of the women who received chemotherapy alone went through menopause. It doesn't so any good to add ovarian suppression if a woman has already gone through menopause with chemotherapy. And that's exactly what we're seeing when we look at the survival analysis.

If you start splitting apart the study and you look at women under the age of 40, there's the suggestion that ovarian suppression might be beneficial in addition to the chemotherapy. And there is further benefit associated with tamoxifen. But the problem here is that this is a very small number of patients; this analysis just barely reached what's often called statistical significance. That's a term you'll hear doctors and researchers talk about. Statistical significance is all about being reasonably certain that the result you see occurred because of the treatment that was given and not by chance alone. If something is said to be of borderline significance or not significant, it means that we can't be sure that the result might not have occurred by chance alone.

There has been some additional work done, and there has been a meta-analysis looking at tamoxifen with or without ovarian suppression. This is the key question in the United States because almost all young women [with breast cancer] are placed on tamoxifen for five years. The question is this: is it important to add ovarian suppression? They had 2,144 women in this meta-analysis which, again, looked at tamoxifen versus tamoxifen plus ovarian suppression. In a meta-analysis, you're looking at the results of multiple trials and you're bringing them together.

Here you can see the results. The word "event" means recurrence or death. It's never a word that I've liked very much. It's a term that's used a great deal in medical terminology. You can see that there was no clear benefit achieved with the addition of ovarian suppression here. In women who received ovarian suppression, there were 290 recurrences or deaths. There were 306 in women who did not receive that. That is not a difference that is significant. It is a difference that easily could arise by chance. The same is true in terms of overall survival. But, once more, there was an insufficient number of women under 40, and an insufficient number of women who were receiving this treatment without chemotherapy, to know for sure.

Our European colleagues feel that adding ovarian suppression to tamoxifen is very important. In the United States, it is much more debatable. There are clinical trials going on to answer this question. Next Saturday I'm going to Switzerland for a meeting called the [International] St. Gallen [Breast Cancer] Conference, where European investigators, along with some people from the United States and others from around the world, come together to try to set guidelines that are broadly used in Europe. You can



be sure that our colleagues in Europe will push for ovarian suppression to be part of the standard treatment. Once again, in the United States it remains less certain.

What are the problems with the studies? I've talked about some of these already. The trials that were performed seldom included tamoxifen, particularly in the control arms. Oftentimes the studies that compared ovarian suppression with chemotherapy used what, in today's view, would be somewhat old-fashioned chemotherapy—although the truth is that, in many situations, we don't know that it's inferior chemotherapy. The studies often included women who didn't have estrogen receptor-positive cancers, and this is a treatment that is only going to work in that setting. And they were often underpowered, which means that they were not set up to show us whether or not a small difference could be detected.

What can we say about ovarian suppression? It's clearly effective when it's given as the only therapy. If you know someone with estrogen receptor-positive breast cancer who's stuck on a deserted island and can do nothing but take a shot of Lupron or a similar medication, that's what she should do. It may add to [the benefits obtained with] tamoxifen, but I believe that's still unclear. I sometimes recommend it and use it as a treatment, but I don't use it in absolutely everyone. It's not clear that it adds to chemotherapy, but we still don't know for sure in the youngest of patients.

Importantly, ovarian suppression, like many other treatments, is not without toxicity and side effects. I'm sure that many of you who are on medications that are suppressing your ovarian function are experiencing some of those side effects. It's not something to be used without careful thought. In addition, there may be some long-term health risks associated with turning off a woman's ovaries at a very young age. We really have to make sure that the benefits outweigh the risks. In my view, it is a reasonable treatment to substitute for chemotherapy in selected patients. But I don't think that it should be routinely added when we give both chemotherapy and tamoxifen.

Having said all that, I want to share with you the results of a very recent study. This study is important for a couple of reasons. One is that it demonstrated just how effective hormonal therapy is in young women in the absence of chemotherapy. The second is that it looked at the role of the drug zoledronic acid, which is one of the bisphosphonates, in young women.

Researchers not have been able to conduct this trial in the United States, because at the time the trial was conducted there was still such a push in the United States to give everyone chemotherapy. But that wasn't the case in Europe, particularly in Austria. This is the Austrian Breast & Colorectal Cancer Study Group trial [Abstract: <http://content.nejm.org/cgi/content/short/360/7/679>; LBBBC story on this trial: [http://www.lbbbc.org/content/news/premenopausal-women-taking-zoledronic-acid-with-hormone-therapy-may-live-longer.asp?section\\_tag=G](http://www.lbbbc.org/content/news/premenopausal-women-taking-zoledronic-acid-with-hormone-therapy-may-live-longer.asp?section_tag=G)]. It looked at the use of ovarian suppression with either tamoxifen or anastrozole, which is an aromatase inhibitor, in premenopausal women with ER positive breast cancer, and it also randomized women to receive either zoledronic acid or no treatment. So it looked at the addition of one of the bisphosphonates. I'm sure that many of you are familiar with these and have read about them. These are the drugs that many people, particularly older women and some men, take for osteoporosis. They're also the drugs that we give women who have metastatic breast cancer to the bone to prevent bone complications.

Importantly, only about 5 percent of the women in this study received chemotherapy. In spite of the fact that virtually no one, therefore, received chemotherapy and that about a third of the patients had stage II breast cancer—meaning they had either larger tumors or lymph node involvement—when they looked five years out, they found that 6 percent of the women had had recurrences and only 2 percent of the women had died, either from breast cancer or from other causes. Those are pretty strikingly good results for a group of patients who received hormonal therapy alone.

I should mention that there was no benefit to giving anastrozole, an aromatase inhibitor, instead of tamoxifen. It is clearly a medication that, when given in this setting, is harder for women to tolerate. Based on the results of this trial, I would argue that it should be used only in clinical trials or for the rare patient who, for one reason or another, simply cannot tolerate tamoxifen. But, importantly, this study also suggested that there was a benefit to giving zoledronic acid. The brand name is Zometa. Again, it's one of the bisphosphonates.

You may say, "You know, Eric, those curves look pretty close together. Doesn't that mean that it's a very small difference?" The truth is that it is a small difference. [We see] about a 3-percent

improvement attained by giving all women zoledronic acid. Wouldn't it be nice if we knew ahead of time which women would make up that 3 percent of women so we could spare everyone else the side effects?

Based on this trial, some people are giving zoledronic acid to young women who are getting ovarian suppression. Not everyone is doing that, though. This slide simply shows that, of the recurrences that were prevented, they weren't [all] recurrences that [would have occurred] in bone. They [would have occurred] in a number of places. This is one of the puzzling aspects of the study.

Should all women with breast cancer receive zoledronic acid? At this time, I don't think everyone should—certainly not now; maybe not ever. The treatment was reasonably well tolerated, but it isn't entirely without side effects. You may know that some people get this flu-like syndrome after taking it. You don't have to watch TV for very long to see an advertisement for one of these drugs where they warn you about jaw problems. They're talking about something called osteonecrosis of the mandible [or maxilla], where there's destruction of the bone in the jaw. It's very uncommon, but if it happens it's quite difficult to deal with.

We need additional studies. We certainly need additional studies [on the use of zoledronic acid] in older women before we give it to those women. We need additional studies [on its use] in women who are receiving chemotherapy before we routinely give it in that setting. The one situation in which I would think about giving this drug today is that of a young woman who has estrogen receptor-positive breast cancer and who is receiving ovarian suppression and tamoxifen as her only therapy. In that setting, I think it's reasonable to consider. I might add that [zoledronic acid] has an added benefit: many of those women have significant bone loss because of the ovarian suppression, and it helps to prevent that.

Moving on to an even more controversial topic: What about chemotherapy? Do all women need to receive chemotherapy? My resounding answer to that is no. But this [subject] is much more controversial than a simple "no" would imply.

The benefits of chemotherapy in women who have estrogen receptor-positive breast cancer appear to be the greatest in women who have HER2 positive cancers, where chemotherapy is standard, [and] in women who have high-grade cancers, meaning that the pathologist says that the cancer



looks, under the microscope, like it is an aggressive or fast-growing cancer. That's often referred to as a poorly differentiated cancer. The benefits of chemotherapy also appear to be the greatest in women who have one of these new tests done on their tumors—something like an Oncotype DX, which I'm sure some of you have heard about, or another test called the MammaPrint. These are tests that measure many different genes in the tumor, similar to that green and red map that I showed you before. By profiling the tumor, they give us information about both the prognosis and whether or not there is likely to be benefit from chemotherapy.

The other situation in which chemotherapy is still routinely given is in women who have very large tumors or multiple positive lymph nodes. In that situation, even if we have reason to believe that the chemotherapy might not otherwise be so very beneficial—say, for example, that a woman has a low-grade HER2 negative cancer, and an Oncotype DX test is done and it scores low—even if all of that is the case, when there are multiple positive lymph nodes or a large tumor, there are very few oncologists in the United States or anywhere else who would be comfortable omitting chemotherapy because we're just not sure enough that it wouldn't contribute a little bit of benefit.

Let's talk a bit more about the kinds of patients who might not need to get chemotherapy. These are data from Oncotype DX. Oncotype DX is a test that costs \$3,400. It is a proprietary test. It can't be done in your hospital; it is sent out to this company called Genomic Health. In some ways it's a pretty slick company in that they have sort of figured how to get right into the market, and they're trying to get everyone to order one of these things. But it's also a company that has made a contribution: I think that this test, more than any other bit of information we've had, has helped move American oncologists away from [the notion of] "chemotherapy for all."

They collaborated with the NSABP—the National Surgical Adjuvant Breast and Bowel Project [<http://www.nsabp.pitt.edu/>—a large, cooperative group, and they went back to an old clinical trial in which all women who had node negative, estrogen receptor-positive breast cancer received tamoxifen as their only therapy; no chemotherapy was given. They applied the Oncotype DX test to the tumors that those women had. They conducted the tests by using sections of the old tumors, which had been stored away.

They found that about half of the tumors were what were called low-risk, about a quarter were intermediate risk, and a quarter were high risk. Shown in the black box is the ten-year chance that a woman would have a distant recurrence or a metastasis of her breast cancer based on her Oncotype DX score. You can see that women whose tumors had a low score had about a 7-percent chance of having a recurrence within the next ten years. In contrast, the [approximately] 25 percent of women whose tumors yielded a high score had four times, five times that risk of having a recurrence. It was just over 30 percent.

Of even more interest was the observation that, in women whose tumors had low Oncotype DX scores, —I keep saying "women who had the low score," but it's the tumor that has the score and I want that to be clear: You don't have a low score. It's your cancer. (Laughter) In the same way we talk about treating patients, not treating cancers, but those mistakes get made, and I apologize if I make them. But what you can see here, if you bear with me for a second, is that in women whose tumors had a low score, there was very, very little benefit attained by giving chemotherapy; in fact, none could be seen. In contrast, chemotherapy got rid of almost all the "badness," if you will, that was associated with a high score.

The solid red line pertains to those women who were given tamoxifen alone. You can see that, as the [Oncotype DX] recurrence scores goes up, as you move along the graph from left to right, the risk of recurrence goes up. Go to the blue line now. While there's a gentle slope up, it's much less steep. Chemotherapy there, in women whose tumors have high scores, is actually able to protect against a recurrence. So—in women whose tumors have low scores, the two curves are right on top of each other, suggesting that chemotherapy adds nothing in that setting. In women whose tumors have high scores, there's a big separation between the red and the blue line, suggesting that chemotherapy is exerting almost all of its benefits in that situation.

The subject of chemotherapy in young women is always an emotionally charged one, even among medical professionals. When we sit in our tumor board every Tuesday at 12:00—about 40 medical oncologists, surgical oncologists, radiation oncologists, pathologists are there—the stakes always go up when we're talking about somebody who's 35 or 38. For better or worse—and I would argue sometimes that it might be for worse—everyone's emotional investment in the discussion

goes up when we're talking about a very young woman. I'm always trying to make the argument that we have to not do that; that we have to think with our heads and not with our hearts. But that happens. And you all have a very noticeable impact on all of us as well.

I believe that the tumor characteristics are probably far more important than a woman's age. Clearly, there are more high-grade tumors in younger women than in older women—so, proportionally there are going to be fewer women who can avoid chemotherapy. But there are still quite a few. As shown in the Austrian study, the outcomes with hormonal therapy alone can be excellent. As shown in those Oncotype DX data, in women with node-negative breast cancer whose tumors are small and whose tumors have low Oncotype DX scores, there seems to be almost no benefit to giving chemotherapy.

It always feels like there is more at stake when we're taking care of a 28-year-old woman or a 32-year-old woman or a 38-year-old woman. But it's important to keep in mind that that is true both in terms of preventing a recurrence and in terms of preventing long-term side effects. You have many, many years to live, and you want to live a long and full life, and you don't want to survive your breast cancer only to have another problem related to breast cancer treatment when you're 50 or 60 or 70. While the immediate concern is your breast cancer, we have to be very, very thoughtful about that. (Applause)

Let's talk about HER2 positive breast cancer. And I told you before, this is the area in which we've, perhaps, made some of the greatest strides—although I might amend that and say that getting rid of the use of chemotherapy in some women with estrogen receptor-positive breast cancer has been a really big deal.

HER2 positive breast cancer accounts for about 15 to 20 percent of all breast cancer. It's probably a little more common in young women. About half of the time, the HER2 positive tumor is estrogen receptor positive; about half the time, it's estrogen receptor negative. When estrogen receptors are positive in a woman with HER2 positive breast cancer, we use hormonal therapy. But there is reason to believe that we should be less confident about the benefits of hormonal therapy in that setting. Historically, there was a very poor prognosis associated with HER2 positive breast cancer. That has clearly changed, both for women with early stage breast cancer and for women with



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advanced breast cancer. The thing that changed that is targeted therapy directed against HER2.

HER2 is a gene, and it's a protein. When we talk about HER2 positive breast cancer, we mean that there are extra copies of the HER2 gene in the nucleus of the cell. That leads to excess production of the HER2 protein that sits on the surface of the cell. When there's too much HER2 protein on the surface of the cell, those proteins can interact with each other and they can essentially talk to the cell and get it to do things that you, as a patient, don't want it to do. The tumor cell, in response to HER2, grows faster, spreads more, invades more and does all sorts of things that are good for the cancer cell but bad for the person who has it.

There have now been multiple adjuvant trials looking at trastuzumab, or Herceptin, in HER2 positive breast cancer patients. The results have been remarkably consistent across the trials. Essentially, they have shown that, for women that have HER2 positive breast cancer and who receive a year of trastuzumab, or Herceptin, about half of all recurrences are prevented.

This is the result, updated in 2007, from the large trial that was done in the United States that compared Adriamycin and Cytosin and Taxol alone versus that same chemotherapy plus Herceptin in women with largely node-positive, HER2 positive breast cancer [Editor's Note: Link to the original study, published in 2001: <http://content.nejm.org/cgi/content/short/344/11/783>]. You can see a significant separation in the curves and a very sizeable benefit from the use of Herceptin. That doesn't mean it was the fix for everyone. In fact, the four-year follow-up [showed that] 15 percent of the patients who had received Herceptin had had a recurrence by that point in time, demonstrating that we need to do more work. [However,] not only has there been an improvement seen in terms of recurrence rates, but there has also been an improvement seen in overall survival. The difference here is much smaller. But this is particularly important, because any woman who didn't receive Herceptin to prevent a recurrence would have received Herceptin when [the cancer] came back. What this says is that getting the drug earlier is better than getting the drug later.

Of course, Herceptin, or trastuzumab, like all therapies, has some amount of toxicity or side effects. There's the nuisance of coming in every three weeks for treatment for an entire year. There's

the cost that we, of course, all worry about from a societal perspective, although I must say that I tend not to worry about it when I'm talking to an individual patient in the exam room. And there is the potential for late effects, although we have not seen any so far.

The biggest problem with this drug is that about 2 to 4 percent of women can develop cardiac toxicity—specifically, congestive heart failure, so that the heart does not pump as well—as a result of treatment. Generally speaking, that is reversible. And there are predictors of who is more likely to have this difficulty. Women who are older, women who have borderline heart function to begin with and women who have a history of taking antihypertensive medications—which, in my mind, means women who have a history of hypertension—are all at increased risk. For most young women with HER2 positive breast cancer, and particularly for those who don't have any of these factors, the chance of developing heart problems is really very small.

There's been a lot of controversy—you can see that I used this slide in 2008 and that I didn't fix this last night on the plane—there's a lot of controversy about how we define HER2 positivity. I used to believe that it was like a switch that was turned on or turned off; [it's easy to] tell whether you're walking into a bright room or a dark room. Most of the time that is true. But it is clear that there are some borderline tumors, and we're still struggling with what to do in those situations clinically.

This is a sculpture that graced the courtyard in the residential college next to mine about 30 years ago. It's by a guy named Claes Oldenburg, who did these sculptures of colossal objects. The point is that size matters. And it's a very important point. Even in the biologic era, disease burden has a profound impact on the risk of recurrence. By the way, this sculpture is, like, eight stories high; something like that. It's humongous.

The point I want to make is that you will hear that all HER2 positive breast cancers are bad and that all triple-negative breast cancers are worrisome. And maybe they are more worrisome than some other cancers. But if you're lucky enough to catch a cancer when it's two millimeters in size and the lymph nodes are negative, that still is very important. For each and every one of these different subsets of breast cancer, [the stage at which] the cancer is diagnosed remains a very important feature, and it should affect how we

think about therapy. A woman who has a small HER2 positive breast cancer is at much lower risk than a woman who has a four-centimeter cancer with a number of positive lymph nodes. And our treatments need to be different.

We are conducting a large trial, in fact, in which we're trying to back off a little on the treatment given to some women with HER2 positive breast cancer—specifically, on treatment given to women with small, node-negative cancers. [In those women] we're giving just 12 weeks of the drug paclitaxel, or Taxol, with Herceptin. We hope to demonstrate that this more abbreviated treatment is effective.

I mentioned that 15 percent of women had recurrences of breast cancer four years later, in spite of treatment with chemotherapy and Herceptin. Of course, we need to do something about that. And large trials are being conducted to try to find new and better treatments. One or more of you may be a participant in this trial, which is being done around the world, including in the United States [[http://www.lbcc.org/content/clinical-trial-examines-optimal-treatments-for-her2-positive-early-breast-cancer.asp?section\\_tag=G](http://www.lbcc.org/content/clinical-trial-examines-optimal-treatments-for-her2-positive-early-breast-cancer.asp?section_tag=G)]. It's a trial in which all women with HER2 positive breast cancer receive chemotherapy. Some receive trastuzumab or Herceptin. Some receive lapatinib, a newer, oral drug; its brand name is Tykerb. And some receive both, either both together for the entire year or sequentially.

In my view, this isn't the best study. It's a study that I support, but it's not the best because, in truth, the women I would like to see enrolled in a study like this are the 15 percent who didn't do well enough with the last treatment. I worry that we will simply add more and more treatments on, in some cases to women who don't need them. I think it's all about individualization.

There are many unanswered questions about HER2 positive breast cancer. We still don't know the very best duration of trastuzumab. Do we have to give it for a year? Can we give it for [a shorter period of time]? Is longer better? There are studies going on that are looking at that. Do patients with very small tumors and negative lymph nodes need the same treatment that others receive? In general, we haven't seen frequent late recurrences, meaning beyond five years, with HER2 positive breast cancer. But, with the use of trastuzumab, are we curing all women who are not having recurrences? Or are we, in some



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cases, shifting when the recurrence occurs? I think we're probably curing most people, but we need more time to sort that out.

We need to find out who needs more than the current therapy. And perhaps the single most burning question in the United States, for a variety of reasons, is what kind of chemotherapy we should be preparing with trastuzumab. On the West Coast there is a tendency to avoid drugs like Adriamycin because of concerns about cardiac toxicity. On the East Coast those drugs are much more commonly given. And there isn't a final answer.

There are many, many new drugs for HER2 positive breast cancer. I mentioned lapatinib, which is a drug that's now improved. All of these other agents are being actively investigated for HER2 positive breast cancer.

I don't usually quote myself, but I did this for a very specific reason. In 2006 I stood up at an education session that I had the privilege of chairing at the American Society of Clinical Oncology [<http://www.asco.org>], and I said what is on this slide: essentially, that I thought we could prevent death from HER2 positive breast cancer. It doesn't mean that absolutely every woman will be cured. Some of those women may be living with HER2 positive breast cancer as a chronic illness. Don't get me wrong: I don't think a chronic illness is a great thing. I think it's much better to be cured than have a chronic illness. But I think that we will have those tools in the next decade because of our understanding of the biologic underpinnings of HER2 positive breast cancer [and] because of the investment of academic researchers and drug companies.

I think that our biggest challenge is going to be making sure that we can deliver those treatments to people because, of course, if you can't get the treatment because you're poor, you don't have insurance, you don't have education, you're from a minority background—I could go on and on about all the things that make people at risk for disparities—but if you can't get the treatment, you can't benefit from it. I should give Susan G. Komen for the Cure [<http://www.komen.org>] credit for opening my eyes to that. I have always viewed myself as a good, progressive doctor who thinks about the needs of lots of people in our society. But I have to say that, since I've been involved working with [this foundation], I have really had my eyes opened in terms of the whole issue of disparities. It's no secret issue, but it is just striking.

One can only imagine how many of the 40,000 deaths a year in the United States could be prevented if every woman in the United States had [access to] the same care that my wife could receive [as someone who's] living in a city, [is] married to a physician, has health insurance and has an education. (Applause) Thanks.

[Let's talk for a few minutes about] triple-negative breast cancer. This accounts for about 10 to 15 percent of all breast cancers that we see in the United States. It's more common in young women, it appears to be more common in African-American women and it's more common in women with BRCA1 mutations. Some very recent data—I was reading about it in a paper last night—indicates it actually may be more common in young women who are substantially overweight. And it may turn out that the connection with African-American women has nothing to do with the genes that an African-American woman was born with and everything to do with the social milieu in which she was raised. Hormonal therapy and trastuzumab are ineffective for these tumors. Chemotherapy is effective, and improvements in chemotherapy have been particularly important in the setting of triple-negative breast cancer.

This is the prototypical triple-negative, sometimes called basal-like, breast cancer. I show this just to point out that these tend to be high-grade tumors. They are estrogen receptor and progesterone receptor negative. When people measure estrogen and progesterone receptors, they apply a stain that turns the cells brown. What you can see under B is an estrogen receptor negative stain. That little bit of brown is a positive control in normal breast tissue that's around it.

We know that, in women who have triple-negative breast cancer, the risk of having a recurrence is somewhat higher and that the risk of having a recurrence is higher early on. That's the bad news. The good news is that, if you're a woman with a triple-negative breast cancer and you have reached the five-year point . . . you are probably cured of that triple-negative breast cancer. (Applause) I wish I could say that's true for other subtypes of breast cancer, but this is a subtype of breast cancer in which recurrences tend to happen earlier, not later.

I show this not to dwell on the negative, but to point out that these diseases, these different subtypes of breast cancer, are really different from one another. And they spread to different places. These are the sites of recurrence in a large group

of women with triple-negative breast cancer who've been seen at our institution. Forty percent of these women had a recurrence in the lung as their first site of recurrence. Now, this isn't 40 percent of all women with triple-negative breast cancer. This is 40 percent of women who developed recurrent breast cancer. Forty percent of those women had their first recurrence in the lung. That's very different from patterns that are seen in other types of breast cancer. Only a quarter of these women had recurrences in the bone. Bone recurrences, of course, are much more common in the setting of estrogen receptor-positive breast cancer. I mention this only because it may turn out, as we move forward, that treatment of specific sites is important.

Chemotherapy has been particularly beneficial for those with ER negative or triple-negative breast cancer. This is shown here. You can see this in the left upper graph. The addition of Taxol to Adriamycin and Cytoxan was particularly beneficial in that group of women.

There are a variety of new treatment approaches—I'm not going to go into all of these in detail. These include treatments with angiogenesis inhibitors, like bevacizumab and others, [as well as] what's called EGFR inhibition. EGFR is the epidermal growth factor receptor, which is present in about half of triple-negative breast cancers. There is some suggestion that older chemotherapy drugs, like carboplatin and cisplatin, that are still used for many other cancers may turn out to be useful for triple-negative breast cancer. And there's a class of drugs called PARP inhibitors that has received a lot of attention.

PARP is involved in the repair of DNA. In women who have BRCA1 mutations—who have an inherited predisposition to breast cancer—those women, when they develop breast cancer, typically develop triple-negative breast cancer. And it turns out that the cancer cell relies upon PARP, which is another pathway. Think of it as another road running parallel along with BRCA1. BRCA1 also works by repairing DNA. When BRCA1 is turned off, DNA can't be repaired and the cell uses PARP. In women who have ovarian cancer and who have BRCA mutations, PARP inhibition has been found to be important, and there's a drug that does it.

There are ongoing studies in breast cancer, and some of the results look very promising. The big question is whether those results will be applicable only to women who have BRCA1 mutations, or BRCA1 and BRCA 2 in some cases, or whether



this will be a finding that's useful for all women with triple-negative breast cancer.

This is a situation in which we desperately need more research. I just came from the review of the Komen Promise Grants. We had specifically asked for proposals related to triple-negative breast cancer, and we got a number of them that were very good. We need to understand to what extent triple-negative breast cancer is one problem, or to what extent it is, in and of itself, several different subtypes and different diseases that need different approaches. We need to have a better understanding of the molecular underpinnings of triple-negative breast cancer. We're not as far ahead here as we are with HER2 positive breast cancer or with ER positive breast cancer.

One of the questions that was raised repeatedly in the grants we reviewed, and something that people are very interested in, is [whether or not] there is a way to use drug therapy to actually convert triple-negative breast cancer to ER positive breast cancer. I'm personally skeptical, but there's a lot of work going on in this area. What molecular markers are important, and which can be targeted for drug therapy? This is an area in which there clearly is a very urgent need for both basic and translational research. I would argue that we really need to understand this problem before we start running to the clinic with an endless assortment of clinical trials. We need to understand the biology before we do that. But, at the same time, we need to feel a real sense of urgency.

Where are we going? I think you can see that, even over the past several years, there has been greater individualization of care that is based on tumor subtype; on patient characteristics—not all patients are the same. Women have been telling us this for years, and I think we're finally listening to them. And it is not just about the tumor; it is also about the patient. And it's not just about the biologic characteristics of the patient; it's also about people's preferences. We know that people can choose between different treatments, and those preferences are very, very important. The extent of the cancer remains very important as we individualize [treatment].

Are we there yet? No. But I actually think that, over the course of the next ten to 15 years, we will be in a place where we really do have designer treatment for each tumor and each patient. Now, that doesn't mean that we're going to need 180,000 different approaches each year in the United States. But it does mean that we won't have just one

approach; we'll probably have 20 or 30 different approaches in terms of the way we deal with a new patient who has breast cancer. And that's really what it's going to take, both to cure the disease in the maximum number of women—I hope all women—and to prevent both short-term and long-term complications.

Thanks for your attention. (Applause)

#### WOMAN:

First of all, I just want to say thank you. It was a very informative lecture. Can you speak a little bit about what patients are appropriate for the use of the AIs, such as Aromasin and Femara?

#### ERIC P. WINER, MD:

To my mind, those are primarily therapies for postmenopausal women. For women who are postmenopausal at the time of diagnosis, there are really one of two preferred approaches: one is to receive an aromatase inhibitor as initial therapy, and the other is to receive a couple of years of tamoxifen followed by an aromatase inhibitor.

In a younger woman, I think the only situations in which you should use an aromatase inhibitor are on a clinical trial—and there are clinical trials going on—or if, for whatever reason, you can't take tamoxifen, either because you have a history of blood clots or some other major contraindication or because it just makes you feel absolutely horrible—although an aromatase inhibitor may do that as well. And if you take an aromatase inhibitor, you have to be absolutely certain that your ovaries aren't working or it will do no good.

Finally, and importantly, there are a reasonable number of young women diagnosed with breast cancer who get five years of tamoxifen and, at the end of five years, either because they receive chemotherapy or because they're just now older, have gone through menopause. At that five-year point, based on the results of clinical trials, it's reasonable to use an aromatase inhibitor [with those women].

#### WOMAN:

You said that getting the Herceptin earlier is better than receiving it with a recurrence. Are there any studies, or is there any information, on HER2 positive patients who are, let's say, eight years out and who did not receive the Herceptin because it was not being given at that time—on them receiving it at any time, at this point, without having a recurrence? Are they doing anything with that?

#### ERIC P. WINER, MD:

It's a really good question. There aren't any [studies]. If you're a woman who is eight years out from a HER2 positive breast cancer, it is extremely likely that you're never going to see that cancer again because HER2 positive cancers, like triple-negative cancers, tend to come back in the first five years. So that's good. (Applause)

A study was done that looked at lapatinib, or Tykerb, in women who had previously had treatment for their HER2 positive breast cancer and who hadn't received Herceptin. They allowed people who were up to a number of years out to enroll. The study closed, and no results have been reported. I would certainly not be in a rush to take a year of Tykerb until those results are available, and I don't know what the study will show. I think that, particularly if they had a lot of women who were many years out participating, [the results will indicate that] the chance that a woman is going to have a problem is so low that the benefits are going to be tiny.

#### WOMAN:

I was just wondering about the role of family history, race and FSH levels in making a decision about chemotherapy protocols.

#### ERIC P. WINER, MD:

Does everybody know what an FSH level is? FSH stands for follicle stimulating hormone. [There] is a blood test [for it] that can give you a snapshot as to what your ovaries are doing at this moment in time, meaning it can tell you whether or not you're in menopause, although [the snapshot is] something that can change. I don't think that would impact my decision about chemotherapy at all because I don't think that we should be necessarily be making different decision in premenopausal versus postmenopausal women.

I don't think that race would affect it to any extent. And I don't think family history would necessarily affect it. Many women say, "My mother died of breast cancer. Should I receive different treatment because of that?" I'm not aware of any inherited predisposition to a bad outcome with breast cancer. I think it's really based on the characteristics of the cancer more than anything else; that and your preferences.

There are some people who say that if I can't tell them there's zero benefit [to a particular treatment], then they want that treatment. No matter how hard I may try to convince someone that that the risks are greater than the benefits, it's



really what she wants. And that's okay in many situations. It really is about one's level of comfort with different types of risk. My job as a doctor is to try to educate people about that and to try to make a decision with people.

**WOMAN:**

What is the benefit, or is there any benefit, of taking goserelin if you are unable to take the tamoxifen?

**ERIC P. WINER, MD:**

If you can't take tamoxifen and you're a premenopausal woman, I would recommend taking ovarian suppression. The question would be whether to do that by itself or with an aromatase inhibitor. I think that, in both the United States and Europe, someone who couldn't tolerate tamoxifen would probably try to do it with an aromatase inhibitor, but the truth is that we don't know that that's better than just giving the ovarian suppression by itself. My own approach would be to start the ovarian suppression and then to add on the aromatase inhibitor after a few months to see how you tolerated it.

Some of you may be on this, but one of the hardest hormonal therapies for a woman—particularly a very young woman—to tolerate is ovarian suppression and an aromatase inhibitor. I describe it as not the dive into menopause, but the deep dive; the plunge into the depths of menopause. And that's a hard thing. Not that I've experienced it. (Laughter) But it's really tough.

**MODERATOR:**

Thank you so much. (Applause)  
[END OF TRANSCRIPT]