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Menopause and Mental Pause: Managing Side Effects

February 23, 2008

Patricia A. Ganz, MD

MARCIA STEIN:

Hi. My name is Marcia Stein, [and I am the chief executive officer of the Young Survival Coalition; <http://www.youngsurvival.org>]. I'd like to welcome you to today's session on "Menopause and Mental Pause." We want to get started so we can get in as many questions as we can in this short period of time.

It's my pleasure to welcome Dr. Patricia Ganz, a professor at UCLA Schools of Medicine and Public Health. She's the director of the Division of Cancer Prevention and Control Research at the Jonsson Comprehensive Cancer Center, which directs the UCLA Family Cancer Registry and Genetic Evaluation Program. Dr. Ganz is a pioneer in the assessment of the quality of life of people with cancer, and she is active in clinical trials with the National Surgical Adjuvant Breast and Bowel Project. She has focused her clinical and research efforts on breast cancer and prevention. She was a member of the National Cancer Institute Progress Review Group on Breast Cancer.

Her areas of research include cancer survivorship and the [late effects of] treatments, cancer in the elderly, and quality of care. She is the associate editor of the *Journal of Clinical Oncology*, the *Journal of the National Cancer Institute*, and *CA: A Cancer Journal for Clinicians*.

I would like to personally welcome Dr. Ganz. As a person who has been through chemo and who routinely says, "Oh, it must be chemo brain, because I can't remember what day of the week it is," (Laughter) I think this is an important topic for all young survivors and something we all deal with. (Applause)

PATRICIA A. GANZ, MD:

Thank you all for coming. What we're going to talk about today is really focused on what happens with breast cancer and menopause and mental pause, as the title says here. You're in the boat with the rest of the women in the world in

terms of having something in common that we experience. We've learned a lot from breast cancer survivors in terms of the manifestations or the experiences that women have from both of these issues, because they get very compressed by going through menopause early and in a rapid way, with the chemotherapy or the surgery that we have. You have really taught the world a lot, unfortunately, by the kinds of experiences you've had. I'm going to share some of that with you in the beginning of my talk, with some information from the NIH State of the Science Conference on menopause.

What I also want to do today is try to provide to you an understanding of women's health and physiology, what's normal, what happens to women as we all age and go through our reproductive life, and then what's really special about breast cancer and how it kind of interacts and perturbs the system, and why you may be experiencing things at a time in your life when you really don't expect to be experiencing them. That's kind of the big picture.

I want to start out with this consensus statement from a State of the Science Conference that the National Institutes of Health had in 2004. This was actually published in 2005. This particular conference got pulled together because of the results of the Women's Health Initiative Study in 2002, which showed that hormone therapy at menopause with estrogen and progesterone, and with estrogen in women who had had their uterus removed, did not confer the benefits that everyone thought. Leading up to that time, women were being prescribed hormone therapy at menopause to prevent heart attacks, to prevent strokes, to help their bones, and to help with symptoms of menopause. But it was thought, because heart disease was the leading cause of death in women – I in 2 women will die from heart disease; it's much lower for breast cancer – that if we could give a drug hormone therapy, either estrogen alone or estrogen combined with

progesterone, for women in those years we could put off a deadly killer.

That's what the medical community was doing until a randomized controlled trial was started by the NIH in the early 1990s that didn't come into fruition until early 2000, and all of a sudden we learned that hormones at menopause didn't stop heart attacks and, in fact, contributed to early deaths in the women who took the hormone therapy. It did not prevent stroke. It did not prevent other cardiac events. It did a little bit with handling some of the symptoms in sleep. That was a little bit better, but many of the women who were in this trial didn't have a lot of menopausal symptoms. It did some good with the bones, but, importantly, it increased the risk of breast cancer, particularly in the hormone-combined therapy with estrogen and progesterone.

In addition, there was a very detailed study looking at cognitive function in the women who were taking either estrogen and progesterone or estrogen alone, and it found that the hormone therapy actually made cognitive functioning worse. All those myths that estrogen was good for the brain, and even some little randomized trials, were not proven to be beneficial. There was a dramatic drop-off in filling of prescriptions for hormone replacement therapy as a result of that. Then we had 50 million or 60 million women in the United States or millions every year crossing into menopause having hot flashes, vaginal dryness and saying, "Woe is me. What can I do? What am I going to do?"

Fortunately, we had a lot of information about women just like you who have been suffering, estrogen-free, with hot flashes and mental changes and other things. In fact, what we had learned and had pioneered in a lot of research that's been done could then go to women who hadn't had cancer, so that's a cross benefit. That's just a little aside.

I want to do these definitions so you all understand that we're all on the same page when



we start to talk about menopausal symptoms. Menopause is the permanent cessation of menstrual periods. Many women have few or no symptoms. The permanent cessation, in general, for women reaching menopause around age 50, 51, is defined as not having a menstrual period for more than a year. Some women will start to have irregular periods. Maybe they will have them every two months, every six months. But until she really hasn't had a menstrual period for a whole year, we don't consider her to be in menopause. Even then, sometimes women will have another period 13 or 14 months thereafter.

Many women in the general population cross through this period of time with no symptoms because they have the lead-up to this, in what we call the perimenopause or the perimenopausal transition, in their 40s – slowly having menstrual and ovulatory cycles where they may actually bleed, and they think they have a period and they've ovulated, but, in fact, they haven't. We call this the perimenopausal transition. Many women will have a preview of what it's like because they will have some months when their hormone levels are very low and they feel that they can't sleep; they feel miserable, and then the next month they get their period and their hormones are okay again.

A colleague of mine who does endocrine menopause care says we call this endocrine chaos. This is exactly the reverse of puberty. So, when the hormones are kind of getting warmed up in our teen years and we're trying to get our regular periods, they're all over the place, both in the girls and the boys. Then they get regular, and then in our 40s normally, they kind of wind down and there's this same period of time. But many women then, when they actually have that last menstrual period, won't have a lot of symptoms. There are a variety of reasons.

They also called attention in this consensus statement to pre- and perimenopausal women who have menopause induced by surgery, chemotherapy or radiation, and that they are likely to experience bothersome or even disabling symptoms. That's really what we're going to talk about today. They concentrated on hot flashes, night sweats and vaginal dryness, which are clearly linked to having lower levels of estrogen in our bodies. There is some confusion or uncertainty about not sleeping, if not sleeping well is really a menopausal symptom. The three that we want to focus on are hot flashes, night sweats and vaginal dryness.

In addition, they talked about alternatives to estrogen. However, their effectiveness and long-term safety needs to be studied. This is, again, for the general group of women, but also for breast cancer survivors. Much more research is needed to clearly define the natural history of menopause-associated symptoms and effectiveness and safety of treatments for bothersome symptoms. This is for the world out there, who really didn't know anything about what they could do other than estrogen. We had already been investigating some of this in breast cancer survivors. I think breast cancer doctors do a lot better job in trying to address this because we've been dealing with it for a while.

Who are the patients that the oncologists see? Well, we used to see women who had recently stopped their hormone therapy because they actually were diagnosed with breast cancer. All of a sudden, they went cold-turkey off their hormones when that mammogram became abnormal, and they had their breast biopsy. We also see postmenopausal women who are treated with aromatase inhibitors, which, again, don't cause hot flashes as frequently as tamoxifen, but still do, particularly in women in their early postmenopausal years.

Highlighted in the aqua color here are you all, which are premenopausal breast cancer patients. Again, what we do, unfortunately, with our treatments is we cause you to go in menopause, which is treatment-induced amenorrhea. I would say it may not be menopause, but we've made you stop menstruating for a period of time, and you have all of the symptoms that one would have if your ovaries weren't functioning. We can give you tamoxifen or ovarian suppression therapy, which can also contribute to this. In some women, your ovaries will be removed perhaps for prevention, if you happen to be in a family where you have a BRCA1 or BRCA2 gene or for other reasons. So this is really you, as my target here today to really share this focused expertise.

I also take care of a lot of high-risk women who are receiving endocrine therapy for chemoprevention. We use tamoxifen and raloxifene for prevention of breast cancer. I also take care of BRCA1 and BRCA2 gene carriers who may have their ovaries removed for prevention of breast cancer and prevention of ovarian cancer. There's a spectrum of women with a breast cancer history or problem who really need our help.

I'm going to talk about hormones in the development of breast cancer, so you'll understand why this is such an issue in terms of giving back estrogen to women with breast cancer; therapy targeted against the estrogen receptor; menopausal symptoms, particularly in younger women, so it's targeted to you and it's focused on your needs; and then, briefly, some of the management strategies. I suspect we'll talk more about this in the question-and-answer session. The latter part of my talk will be on the cognitive issues.

I want to talk about who gets breast cancer. This list is probably familiar to you, but I'm sure that if we went around the room, many of you would say "I have none of these risk factors." Breast cancer, unfortunately, occurs in young women without a cause. Maybe one of these days we'll understand some of the other reasons why. Clearly, if you have a family history, that would be very important. If you had early menarche, that would also be important, because your breasts were being exposed to your own hormones early. Clearly, there is some risk of having a late pregnancy or no children at all, but it's relatively weak in terms of the risk factors. For younger women, this doesn't explain very much. For the average woman who gets breast cancer at age 61, she may have experienced all of these things. Yes?

WOMAN:

Is that what nulliparity ...

PATRICIA A. GANZ, MD:

Oh, sorry. Nulliparity means no children. I apologize. I should go back to this. For early menarche and late menopause – this is the way I've been explaining it to high-risk women lately. If we ask somebody about how long they had smoked, how many years they had smoked, and how many packs per day they smoked – say, if somebody smoked for 20 years and they smoked two packs a day, that would be 40 pack years of exposure to the tobacco. We would say that has a certain risk of lung cancer or some other diseases.

Well, it turns out that for breast cancer, 80 percent of the women who get breast cancer have no family history, have no specific risk factors other than just being a woman, and the risk factors they have are the exposure to their own ovarian hormones. That is when cancer is started. In most women, it's expressed in later years. If you start to menstruate at age ten and you go through menopause at 55, that's 45 years of exposure to your estrogen and progesterone from your ovaries.



But if you started to menstruate at 15 and went through menopause at 45, that would be 30 years. When we're seeing largely older women, it's this long-term exposure, starting to menstruate early and going through menopause later, or taking hormones at the time of menopause, that really extends the risk. For all of you, you haven't been at it long enough in terms of your life to say this is a contributing factor.

WOMAN:

Does the birth control pill . . .

PATRICIA A. GANZ, MD:

Birth control pills of the low-dose variety do not seem to be a risk factor, because those hormone levels are actually lower than what your own estrogen and progesterone would be from your ovaries. You're still getting exposure of your breast tissue; it's not like we're taking it away. Women who have their ovaries removed in their 20s or 30s for some other reason have practically a zero chance of getting breast cancer. It is the repetitive cyclic exposure of the breast tissue to estrogen and, most importantly, progesterone – in the breast it's progesterone that probably initiates the cancer, and estrogen that maintains it.

If we didn't have ovaries, life wouldn't be good for us. It wouldn't be something we'd want to do, but it is, again, that repetitive cyclic exposure of the breast tissue that plants the seeds. I have another slide later that will set the stage, and you'll understand why most breast cancers are started in our premenopausal life, and then aren't expressed until the 60s, 70s and 80s. Those of you who have gotten it early, if you're a gene carrier, we know why. If you are not, if you've been tested and you're not a gene carrier for BRCA1 or BRCA2, there will probably be other genes that we are going to discover that explain why your breast tissue was very responsive to the estrogen in your body. I'm going to talk about that in a little bit.

This shows the hereditary breast cancer risk: Again, probably 20 percent to 25 percent of all breast cancers have a familial history. The women who are diagnosed may have a family history, but very few of them are related to the BRCA1 and BRCA2 genes. Those genes are also associated with ovarian cancer. That's a very rare cancer: 5 percent to 10 percent of all ovarian cancers are associated with the BRCA1 and BRCA2 genes.

As I've already said, just being a woman is a risk factor for breast cancer. For the few men who are here in the audience, the mirror image for men is

prostate cancer. Just being a man is a risk factor for prostate cancer. It is the male hormones from the testis stimulating the prostate. . . that leads to precancerous changes that can then become a cancer. These are the two leading cancers. About 30 percent of cancers in men are prostate cancer. About 30 percent of cancers in women are breast cancer. Our biggest risk factor is just being a woman or a man. Even some of the things we know about in terms of diet and lifestyle – the way alcohol increases the risk of breast cancer is it raises the blood estrogen level – even that exposure is working through the same internal pathways.

I hope this is information that you know, but if you don't, I'm glad to share it with you. I want to talk about this before we talk about menopause. In the premenopausal woman, over here on the left, you can see the ovaries. That's the major source of hormones. In the postmenopausal woman – we've had a lot of talk today, a lot of questions about aromatase inhibitors. When the ovaries are no longer making estrogen, the main source is over here in the fat tissue and in the muscle. There's an enzyme there called the aromatase enzyme. The primary source of male hormones in a postmenopausal woman, let's say in a 60-year-old woman, is coming from her adrenal glands. In her 50s, she may still have some male hormones coming from her ovaries, but that is not contributing a lot in terms of estrogen production.

The aromatase inhibitor drugs block the conversion in the fat tissue of male hormones to estrogen. You would have a reduced level of estradiol. When you're menstruating, in an average menstrual cycle, your estradiol level is 100 to 200. I won't tell you the units, but that's what it is. When you go through menopause normally, say, a woman in her early 50s, her estradiol level drops from 100 to 200 every month to 20. That's a big, huge drop.

When women were taking hormones at menopause, they were continuing to keep their estrogen levels up, maybe to 70, 80, 100. They weren't dropping them to 20, and they were continuing to get stimulation of precancerous changes in the breast. But when you go through menopause, either having your ovaries removed or going through a true menopause – and we'll talk about the fact that when you take chemotherapy, it may not shut this all down – you're still having some hormones produced by the ovaries.

The aromatase inhibitors only work when there's nothing coming out from the ovaries. Then the estrogen and its metabolites work on the breast

tissue. In the breast, you get response from the glandular tissue, as well as the stromal tissue – the supporting fat and other connective tissue around the glandular tissue. There's probably as much response in that tissue as there is in the glandular tissue. That's what makes your breast dense on mammograms. That's why you all have dense breasts; it's hard to see. Hopefully we're going to find the genes that control that response and make you respond very vigorously to your own estrogens.

Here are some of the markers of exposure to estrogen and the risk of breast cancer. I talked to you about the family history and menstruating over your lifetime and whatever. This is a study of postmenopausal women looking at osteoporosis risk. They were all at risk for fractures. You can see that the highest level of estrogen in this group of older women is around 11. Down here in the lowest third, it's less than 8.6. This is the range. But if you look here on the left, which is the relative risk of breast cancer, even within this group of postmenopausal women, the women who had an estrogen level that was above 11.6 had a five-times increased risk of breast cancer compared with those with low levels. So having higher levels of estrogen, even though this is low compared with premenopause, is significant in terms of the risk of later-life breast cancer.

Similarly – this is not from the same study, but it's been shown that women who have breast density of this sort have higher levels of estrogen. You can see, looking at this mammogram on the left; the black stuff is the fat. This is some of the glandular tissue. This is the nipple. Look at this snowstorm here. This is not just reaction of the glandular tissue, but also of the stroma. The tissue is responding to the high hormone levels and growing in premenopausal women. There's great variability. Two women can have exactly the same blood level of estrogen. One can have fatty breasts, and one can have dense breasts. That is probably partially what's driving the risk of breast cancer in younger women who get it.

This is from an old study. It was the Framingham study, a cardiovascular risk study. They did X-rays of the hands in women, and then looked at the risk of breast cancer over time. These were the women who had the densest bones. The bones are very like the breast. There are enzymes, and there are protein responses in the way the cells respond to the estrogen that's circulating and take it up and react. The women here who had dense bones as young women had a higher risk of getting



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breast cancer later compared with those who didn't. Again, estrogen is good for us. It's good for our bodies in many different ways. It makes us feel like a woman. It's good for our bones. But depending on our own individual tissue responses, we may be at higher or lower risk for breast cancer, at higher or lower risk for osteoporosis. In general, this is related to the level of estrogen in our bodies.

This is an example of what happens when you treat women with hormone replacement therapy at menopause. This is a woman before she went on hormone therapy. You can see it's mostly fatty tissue and some glandular tissue. Look at what happened after she had been on three years of hormone replacement therapy, raising her blood estrogen level and her tissue responding. This is the biology of breast cancer. Based on this largely epidemiological data but also on information from the Women's Health Initiative [prevention study; <http://www.nhlbi.nih.gov/whi/index.html>], we have to conclude that reproductive hormones and these exogenous hormones, the ones you take by mouth, have to play a role in the initiation and promotion of breast cancer.

This is the curve I was just talking about. From the time that we can see a 1-millimeter change on the mammogram – which is pretty hard to see – to the time we can actually see a small tumor at 1 centimeter, this particular cancer, from the first cancer cell to the time we can detect it on the mammogram, has gone through 30 doublings. The average doubling time for a tumor is about 100 days, so to go from one cell to two cells is 100 days; two cells to four cells is 100 days; four cells to eight cells is 100 days. In a year, that tumor has been perking along very, very slowly.

By the time we actually pick it up on a mammogram, 1 centimeter in size, which everyone would say is pretty small, it has been seven years since that first cancer cell. It's a long time. Now, I agree, some tumors may grow faster than others, and I know younger women have that experience. But way out here to the left are the pre-cancerous changes. The whole process of getting breast cancer is like a 20-year episode, 15 to 20 years of these precancerous overgrowths in the breast, and then ultimately a cancer that might be detected. Clearly, when we detect large tumors, they have been there for a longer period of time, but they may have rapid growth toward the end.

This is looking at it under the microscope. Most cancers occur in the duct. You can see these are nice, round, regular cells – but we're beginning

to see overgrowth of cells into the duct. If you did biopsies on women in their 20s and 30s, the average woman, you would see a lot of this in the breast. This is just normal. If we look at autopsy series of women in their 40s who died in auto accidents or some other trauma, we will see a fair amount of atypical hyperplasia and ductal carcinoma in situ, far more than is accountable for the number of cancers that we see after menopause. So, most of these regress. They go away as a woman goes through menopause. Only if she takes hormones or if she's obese and has high hormone levels in her postmenopausal years do these perk along.

Well, you all have gone through this whole trajectory at a much earlier clip. We don't know why, but this is still how you got to getting breast cancer. It's just that for the usual woman, these are kind of sitting there – these precancerous changes are sitting there in the breast. With mammography that we do in the 40s now, we see atypical ductal hyperplasia. It turns up as calcifications. We see DCIS. Some of you may have been diagnosed in this way. If it hadn't been for mammography picking these up, we wouldn't know about it. We don't know that all of them would go on to be serious disease.

With that kind of breast cancer IOI, I want to talk about what happens to you with the treatments that we give. Until recently, the primary treatment for younger, premenopausal women has been chemotherapy. If you look at the 2000 Consensus Conference on Adjuvant Therapy for Breast Cancer, the recommendation is that all women get chemotherapy to treat their breast cancer, and that women who have hormone receptor-positive tumors receive some form of endocrine therapy regardless of age. In the case of younger women with endocrine-positive tumors, that mainstay has been tamoxifen. I'll spend a little more time talking about ovarian-suppression therapy, which is with gonadotropin-releasing hormone therapy or removal of the ovaries.

Up until now, we think all of these do about the same. Essentially, if you take tamoxifen for five years at the breast level, the breast tissue is not seeing the estrogen that's circulating in your body. It's hiding from it. It doesn't let it get in. Your estrogen levels in your blood don't fall; in fact, they actually go pretty high. It's not that you're estrogen deficient, but that the brain, where the temperature-sensing areas are, doesn't appreciate it and, importantly, the breast doesn't. If there are

metastases that may have spread, cells that have spread to other parts of the body, they are going to be stopped dead in their tracks because for hormone receptor-positive tumors, estrogen is the fuel that initiates and promotes and feeds the fire of those cells growing.

If you shut down the ovaries with the injection of Lupron or goserelin, you essentially don't ovulate every month. I have a couple of young patients who are on these drugs right now. Their estradiol levels are around 20, so they're down in that postmenopausal range. They're not getting progesterone out from their ovaries, so their breasts are seeing a much lower level of estrogen. Interestingly, the FSH [follicle-stimulating hormone] is not high in these young women, because that's how the drug works. The couple of patients I've treated lately with this therapy haven't had hot flashes as bad as I sometimes see with tamoxifen.

You can have your ovaries removed, and then you go cold turkey into menopause, which is very, very difficult. Some women choose to do that. It's not something I think I would do for breast cancer treatment in general, but for some of the patients I take care of who are gene carriers, it's certainly a choice that they make.

These are the armamentarium of our therapies. They are good therapies. Triple-negative patients, if they get treated, are going to get chemotherapy alone. Patients who are estrogen receptor negative and HER2 positive are going to get trastuzumab. Trastuzumab does not contribute to menopausal symptoms as far as I know. But it's for those of you who get both the chemotherapy that makes you go potentially into menopause and also the endocrine therapy with tamoxifen that this is an effect. Yes?

WOMAN:

I had a full hysterectomy. Is there a benefit for me to continue to take tamoxifen?

PATRICIA A. GANZ, MD:

I can't comment on your personal situation right now. Why don't we take it later in the discussion, okay?

This is a mixed group – some of you are in the 25- to 30-year-old range, and some of you are closer to 50 and may have been treated in your 40s, depending on where you are in the reproductive cycle. . . . I have a 31-year-old now in my practice. She's finishing up her fifth year of tamoxifen. We're hoping she's going to get pregnant



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after she finishes up. She's menstruating. Everything's going fine. She had chemo. She didn't bat an eyelash. But if you're 42 or 43 – over age 40 – and we give you standard chemotherapy with cyclophosphamide, which is the major culprit, you're very likely to go into menopause. Again, you're all young, but where you are in that trajectory really makes a difference.

This is a study that Dr. Pam Goodwin did where she followed a group of younger women who were all menstruating regularly at the time they started their treatment. This is the risk of amenorrhea, which means stopping menstrual periods for a year. If you look here, these were the women who got chemotherapy and hormonal therapy. Fifty percent of them had stopped menstruating as a result of this treatment if they were at age 35 or 36. If they just got chemotherapy alone, it pushes it up here to around age 40. So, for example, a triple-negative woman being treated at age 40 has about a 50 percent chance of going into menopause or amenorrhea for one year with this. If she's older, if she's 48, she has an 85 percent or 90 percent chance of going into menopause.

Look at this curve here. This is tamoxifen alone. If you are taking tamoxifen alone and you're 45, you only have a 10 percent chance of going into menopause. This is really the fact – that this does not stop menstrual periods. But when we give chemotherapy and your ovaries are injured as a result of the chemotherapy, and then you get tamoxifen, which kind of shuts down the system when they have been injured in this way, you may not menstruate. As we heard from many anecdotes today, though, many women resume their periods two or three years later. That's why we don't want to give aromatase inhibitors to them, because their ovaries are still functioning and putting out high levels of estrogen.

What symptoms occur at menopause? I don't have to tell you. You're pretty much experts in this. These are data from the Breast Cancer Prevention Trial. I did the quality of life for the tamoxifen prevention trial. These were healthy, high-risk women who wanted to participate in this trial. This was their baseline symptom reporting at the time, before they ever went on tamoxifen or placebo. Calling your attention to the women 35 to 49 years of age – about 25 percent of them were reporting hot flashes already. For night sweats, about 20 percent of those 35- to 49-year-olds. Vaginal dryness was reported in about 15 percent of them.

These symptoms are not unfamiliar to women ages 35 to 49. They're just not that common. If you take somebody who's 48 or 49, she's in the latter phases of her perimenopausal transition, so she may be having a lot of these symptoms.

I'll call your attention to the fact that all of these things go up in the 50- to 59-year-old age group, which is when most women are going through menopause. The average age of the last menstrual period is 50. If you look at the women over age 60, they're not having so many hot flashes and sweats. They have a lot of vaginal dryness, and that does get worse with age. This is healthy women. Joint pains are also something that women experience that goes up as they age. These are just normal, healthy women. They hadn't taken tamoxifen or placebo, and they're high risk for breast cancer, so they could be your sisters.

Now, I'm going to compare the symptoms from the BCPT patients I just showed you with women who have been treated for breast cancer. These are survivors who participated in a study that we published in 1998. I've broken it down by age, so I'll call your attention to the fact that for women younger than 50 who are between one and five years out from their breast cancer diagnosis, there's about a doubling of the rate of hot flashes that they report. It also goes up for women over age 50 and also over age 60. Clearly, in this group of women, it's probably mostly chemotherapy. At the time I did this study, very few women were getting tamoxifen premenopausally. Here and here, it's probably more related to tamoxifen.

If we look at night sweats, which are another manifestation of your temperature-regulating systems being abnormal, you can see again a doubling in the women younger than 50 reporting night sweats. It increases as you get older, but for women age 60, not so many. Then vaginal dryness – this is like erectile dysfunction; it's the erectile dysfunction for women. You didn't hear vaginal dryness talked about very much until the Women's Health Initiative [prevention trial] stopped estrogen for hormone replacement therapy for women. Now it's a very big, popular topic, and it is a common one.

Look at the vaginal dryness: As I already pointed out, it goes up as women age, but look at the younger women. This is not something they counted on as part of their cancer treatment. It's about three to four times higher in terms of the comparator group here. Vaginal dryness is certainly an important problem and leads to sexual

problems, pain with intercourse, that concomitant of having vaginal dryness. Only 6.6 percent of healthy women without breast cancer were reporting pain with intercourse, but there's about a five-times increased risk in women who have been treated for breast cancer suffering from this.

Weight gain is also a very important issue. . . . Over the lifetime, this is the biggest risk factor for developing breast cancer, because most women gain weight from age 18 into their 60s and 70s, a couple of pounds a year. In 10 years, you're 20 pounds heavier if you don't watch yourself carefully. We have our metabolism slowing down, and it is really due to a decrease in our hormones that occurs with the menopausal transition, but also throughout our life. We have to be constantly vigilant.

Women who go through menopause prematurely as part of chemotherapy or having their ovaries removed have an increased accelerated weight gain as a result of that. Many of you also gained weight with the chemotherapy, whether it was due to some of the drugs you were receiving, or being less active – it's very complicated, but this is an important problem. You can see that it's common for everyone but a bigger problem for younger women.

This is another survey study that we did. It's not broken down by younger versus older, but I wanted to talk about these symptoms based on the kind of treatment one has. With no chemotherapy or no tamoxifen therapy, women overall – all ages – about 40 percent of them report hot flashes. But you can see, with the combined therapy it goes up. Similarly with night sweats, and vaginal discharge is a side effect of tamoxifen.

If we look at vaginal dryness, again, chemotherapy is probably the culprit. Several studies have shown that chemotherapy significantly contributes to sexual dysfunction and pain with intercourse. Tamoxifen in some women, interestingly enough, gives them some more lubrication, so with the vaginal discharge it may be a mixed bag. It depends on the individual person. But weight gain didn't seem to be significantly different among the groups. That's because all women, no matter where you are and what kind of treatment, have this as a problem.

Then, these were self-report questions, since we're going to be talking about mental pause later. In terms of complaining about difficulty concentrating and forgetfulness, there was really no significant difference by treatment. This is very,



very common, having traversed the menopause in the past few years myself; it's not unusual to have trouble finding words. I may have read something, and I cannot remember it; it was just a few minutes ago. I'm a great multi-tasker, and I'm still able to do that, but I have, as I'll talk about with the chemo brain, seen many women who have had significant problems. But in just this minimal data, there's not much difference by treatment. Here, what you see is the more intensively treated women having more troubles with sexual functioning.

Talking about weight gain and the chemotherapy treatment: This is from a study that Dr. Pam Goodwin did, again looking at an inception cohort of women. If you have any chemotherapy, compared with none, you have a higher risk of having weight gain. If you are still premenopausal – if you didn't go through menopause with your chemotherapy – versus becoming menopausal, you have a lower risk of gaining weight. If you're postmenopausal and, again, this is for older women, it didn't change. There's something about this change in menopausal status that I've already alluded to that accelerates the weight gain as well. And chemotherapy clearly is the main culprit in younger women.

You don't think about weight gain as a menopause symptom, but I do. I want all of you to live a long time, and you may get another breast cancer in the future. The best thing you can do is manage your weight – exercise and be careful about what you eat. You don't have to lose ten pounds in one week. We're talking about weight gain that has crept up over many years. The opportunity to either not gain weight – so you're going to be 20 pounds thinner in 10 years because you didn't gain two pounds a year – or to lose some of that weight is very important in terms of reducing the risk of getting another breast cancer in the future, a recurrence of the cancer, and also in terms of other kinds of health problems.

I want to talk for a second about the risks of hormone replacement therapy. This came from the Women's Health Initiative Study. The combined therapies, as I mentioned, increased the risk of cardiovascular disease, blood clots and stroke. There was an increased risk of breast cancer with estrogen and progesterone – but, interestingly, not with estrogen in the women who had had hysterectomies. Women at any increased risk for any of these conditions should not be prescribed hormone therapy. This is the general population – we recommend for the general population, if we

use hormone therapy, we use it sparingly for a very short period of time.

Now, what about women with breast cancer? Before we had the Women's Health Initiative Study, a number of centers around the world were beginning to treat women with hormone therapy, because the thought was, well, if a breast cancer survivor is going to live a long time, we should protect their hearts, we should make sure their brains are okay, we should treat their symptoms. Then a randomized trial called the HABITS trial was actually stopped early in 2004 because the rate of breast cancer in those women who take hormone therapy was 3.5 times the rate for the other women. Women who had had hormone therapy in the past had an even higher increased risk. An update of this trial will come out in the *JNCI [Journal of the National Cancer Institute]* soon.

Hormone replacement therapy is definitely not good, from randomized trials, in women with breast cancer. Even if you had an estrogen receptor-negative tumor, we do not think it's safe.

What do we do, then, for high-risk women to do this? Based on what I've told you about how estrogen and progesterone are integral to the development of breast cancer over time, we try to avoid this, particularly in high-risk women.

For the carriers, some of you may have sisters who are gene carriers and do not have breast cancer, and they may have had their ovaries removed. Some studies suggest that if they have had their uterus and their ovaries removed, giving back estrogen alone, up until, say, age 50, is okay because we're not extending the prolonged period of hormone replacement. Many of the women I see who have their ovaries out for being a gene carrier – it's pretty bad to go through that cold turkey. A lot of them will choose to take a little bit of hormone therapy for a year or two to get them through that, and that's okay.

What about how you should be managing this? I don't have a lot of slides on this because there is literature and I can take questions on this later, but there are a variety of drugs. Dr. Charles Loprinzi – who has been the primary person doing a lot of these studies at the Mayo Clinic and the North Central oncology group – in randomized, placebo-controlled trials has shown that the drugs colonodine, which is a blood pressure drug that works with the brain, Megace, which is a progestational agent used in the treatment of advanced breast cancer, venlafaxine, which is an antidepressant, and gabapentin, which

is used for peripheral neuropathy, all alleviate hot flashes and sweats.

The important thing for you to realize is that for many women, having bad hot flashes is a transitory thing. Women even in the postmenopausal years who go through it normally may have it for a few years. Or, if you're on tamoxifen therapy and you're getting directed that it's going to be while you're on the treatment, it will eventually go away. There are a certain percentage of women who have persistent symptoms. Often, treatments with these drugs can be for a relatively short period of time to get you through this. There are still people who don't get relief, and it's difficult. I have even given estrogen to women short-term for this situation.

Vaginal dryness, as I've told you, is very common as women age anyway. There are vaginal moisturizers, such as Replens, which in randomized trials have been shown to improve pain with intercourse and improve sexual activities. A study we did actually showed that. You can also use lubricants such as K-Y Jelly or Astroglide, which can be used at the time of intercourse and are very effective in decreasing discomfort with intercourse.

There are two low-dose vaginal preparations that I use in my practice. I tend to prefer the Estrin, which is an estradiol-impregnated, low-dose ring that sits in the vagina for a three-month period of time. You can check the estrogen levels for the woman. Remember, I talked about the fact that your estrogen should be at a certain level. In fact, with this particular preparation, it tends to stay down in the postmenopausal range. I've only given this to women, typically, if they're on tamoxifen, because they have high levels of estrogen or higher levels of estrogen anyway if they're on tamoxifen and premenopausal.

A bit of extra estrogen from the vagina doesn't make a difference. If a woman is on an aromatase inhibitor, though, it is a problem, because with something like Vagifem, it can raise your blood estrogen levels to 20 or 30. Remember, the goal in the postmenopausal state is to bring the estrogen level down to the zero if you're using an aromatase inhibitor.

In summary, these kinds of symptoms are something that the whole world of women has to deal with. It's not fun getting old, I can tell you that. These are common symptoms that everybody has to deal with now that hormone replacement therapy is not the normative thing to give. You need to talk to your doctor about these problems.



You need to find somebody in your community who can help you with these symptoms. For some of you who are young, you may have transient, passing-through menopause, if you will, with all of these symptoms, and then your periods may come back. You'll be out of the woods, in a sense, in terms of symptoms. If not, you need to look for somebody who can help you with this.

Again, the nonhormonal therapies are what we should use first. Very rarely, with people whose lives are completely miserable, I have given low-dose estrogen. I prefer to do that rather than taking some herbal remedy, because I know exactly what you're getting and we can measure your blood level and know exactly what's going on. The main thing is to just do what is necessary for the symptoms.

I also give testosterone to patients. I didn't talk about that a lot. If your ovaries completely shut down or if you have them removed, you may have no testosterone. Your interest in sex may be disappearing or gone, and testosterone replacement in low doses may also be useful for that. But many symptoms will improve over time.

I want to talk now about mental pause. I really want to say, "Does chemo brain exist?" Because I'm not sure it does. I'm actually funded right now by the National Cancer Institute to do a large study where we're taking women after chemotherapy before they start their endocrine therapy. I think the endocrine role in what's going on, as I've talked about menopause, may lead to some of the mental changes that women complain of. We're going to be following about 250 women as they start their hormone therapy, or not, and looking at them with very detailed studies. We don't have enough information on this.

Patients typically will report problems with thinking and memory while they're on chemotherapy. But a lot of them are on Ativan and a lot of other premeds that kind of make them loopy, and they may not be sleeping at night. If you're not sleeping and you're anxious, it's very hard to concentrate on what else needs to be done. That's usually why you bring a friend with you to your treatments.

Some of these symptoms persist, and women may have continuing problems afterward. This also may be associated with chemotherapy-induced menopause. If you're having hot flashes and sweats and not sleeping all night as a result of this, it's hard to feel really sharp the next day. I can speak to this myself. I had ... night sweats and was not sleeping, and I was not sharp. Good thing I wasn't

a doctor in the operating room. I could get around and do what I needed to do, though. This is, I think, part of what goes on when you're having these usual menopause symptoms, and I certainly didn't have chemotherapy.

These self-reported deficits are not always associated with performance abnormalities on neuropsychological testing. Most women – we actually do fancy neuropsychological tests where they have to remember things and do things, draw figures and so forth – actually do pretty well, so there's this disconnect between what women complain of and how they actually test. Some people have said we shouldn't call this chemo brain; we should call it cancer treatment-associated cognitive complaints. (Laughter) It's easier to call it chemo brain, but not everyone who has these complaints – some of the patients I've seen have only had hormonal therapy. They haven't had chemotherapy.

This is a complicated slide, but this is kind of a current working idea of what may happen that leads to altered brain and/or cognitive functioning. You can think about the seed being the cancer, the soil being what you bring to this. As you know, we're all worried about getting Alzheimer's disease as we age. In our population, there's something called the APOE e4 gene, which may be associated with an increased risk. There's some suggestion that patients who have this abnormality may be predisposed to having more injury from the cancer treatments that we give.

You can talk about the therapy as being pesticides if you want. This leads to inflammation, vascular injury, the hormonal alterations that we've talked about, a lot of other things that can also influence how we think and function. These are the ways we can actually look at things: We can give people fancy neuropsychological tests, we can do EEGs, and we can image their brains.

Why is this important? Well, we have more survivors than we've ever had. There are about 2.5 million women who are survivors of breast cancer. They're like you. They're doing all of their everyday activities. They're trying to live a full life. It can have an important effect on what they do, so this is an important area for investigation. We need a lot more accurate information, though, because I don't want you not taking potentially life-saving treatment for your cancer because you're afraid, "Oh, I'm going to have chemo brain."

I've had patients whom I've seen for consultations, and I think the true incidence of

this being a problem may be 10 percent to 15 percent. In some of the studies now where people have done neuropsychological testing before chemotherapy is given, as many as 15 percent to 20 percent of patients already test abnormally on the neuropsychological test. (Laughter) And some of them get better after treatment. We're not going to recommend chemotherapy for that.

Some of the earliest studies related to this were related to high-dose chemotherapy, which a lot of young women got. This first study by Fritz Van Dam from the Netherlands was part of a study where women were getting high-dose chemotherapy or standard-dose chemotherapy with tamoxifen, or early-stage breast cancer without any chemotherapy or tamoxifen. They did very elaborate neuropsychological tests about two years after their diagnoses, and what they found was that the women who got the high, high dose – bone marrow transplant-level doses – did have more impairment compared with the women who didn't get any treatment at all.

We have done some similar work with women who were longer-term survivors, two to five years out after diagnosis. What we see in these kinds of tests are very subtle abnormalities that seem to be related to [treatment with] chemotherapy plus tamoxifen, and self-reported complaints don't seem to connect. These are the two areas: visual memory and visual spatial problems. I want to show you here: verbal memory.

These are breast cancer survivors who didn't get any chemotherapy or tamoxifen, and they are higher functioning than the general population in verbal memory. That's because breast cancer patients and survivors are higher socioeconomic status, and maybe they're high performers. All of these scores are not that impaired, but subtle differences in their ability to do some tasks are something they really notice because they're high performers to begin with. This looks at all the scales together. My hypothesis is that tamoxifen and the hormonal therapies we give are probably playing some role in this added dysfunction.

Some of the other studies we're doing look at PET scanning. I'll show you some of that data. We're looking at the relationship between fatigue, sleep and cognitive functioning. This is a PET scan set of images. This is a woman without a breast cancer history, age 51; a woman with breast cancer who didn't get any chemotherapy; and this is a single woman who got chemotherapy. If you look at the frontal part of the brain here, up at the top,



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it's kind of red and orange in both of these women. But here, it's kind of cool green. There's another area here that's more cool green.

What we see is a difference in metabolic activity in women who have chemotherapy, in the frontal area and also in the Broca's area, which is the speech area, suggesting that the metabolism has changed, possibly as a result of chemotherapy. This is another way of looking at the uptake. The PET scans basically show glucose metabolism in the brain. If we look at a group of women who got chemotherapy versus those who did not, we see that there's less uptake in that superior frontal gyrus and in the Broca's area.

This is a test, one of the neuropsychological tests, where the women were presented with this figure and then asked about five minutes later to copy it. I was one of the first test subjects for a neuropsychological battery, and I can tell you, it's not easy. It's not a figure you would remember; it does challenge you. What we find is that the poorer the woman did on that recall task in the neuropsychological testing setting, the lower her activity in the brain. There seemed to be some relationship between what we were seeing on the brain metabolic study and her performance.

If we group all those women together – this is a larger study that was published in *Breast Cancer Research and Treatment*; it's cross-sectional. These are all women who were treated probably five, six, seven years ago. We see differences in these areas. When we had these women do a memory task during the PET scanning episode, the women who had to do this memory task had relatively little activation of these parts of their brain. The women who had chemotherapy had to pull on many other parts of the brain to do the same tasks. I'm going to show you a picture. This is from a study that was published in the *Journal of Clinical Oncology* just last year, with a patient who was participating in a chemo brain study and her twin sister, who didn't have breast cancer, didn't get chemotherapy – identical twin, genetically completely identical. Neither of them complained of any problems with memory. But you can see, trying to do a memory task in the scanner – this is an MRI now – at each step of the tasking, this woman had to pull on more parts of her brain to get the same response that her identical twin did.

We do believe there are some changes. What we need now are these prospective studies that look at this to say, well, how much of this was just because the woman had some changes in her brain

already? How much was because of the chemotherapy? How much was because she went into menopause? How much was because she got tamoxifen? How much was because she got an aromatase inhibitor?

In the study I'm doing, we're measuring blood hormone levels. We're measuring inflammatory markers, cortisol, stress response, looking at sleep problems, looking at a gazillion things, as well as doing the neuropsychological testing and the brain imaging. We hope to have some answers in a few years to try to explain this. There doesn't seem to be a relationship between menopausal symptoms and cognitive performance in several studies.

This is an interesting study that was done in England, where they did a prospective study, kind of the gold standard, looking at women before they started adjuvant treatment, and a control group of women who didn't get chemotherapy, women who didn't have breast cancer. They gave them neuropsychological tests, and there was absolutely no difference between the chemo patients, the non-chemo patients and the controls. What they did find, though, was that treatment-induced menopause was associated with a significant change. So, how much of what women are complaining about is really bound up with menopause versus being a toxicity of the chemotherapy? We don't know.

A lot of what we're trying to do in some of our research in my laboratory is to look at other things that might make some people susceptible to this, by looking at some of the inflammatory pathways and the mind-body connections. We have been able to identify some women who are persistently fatigued after breast cancer treatment who have abnormalities in their immune system, and it's kind of revved up. We have higher levels of the immune factors in these fatigued women. We see depressed cortisol in these women who have persistent fatigue after their breast cancer treatment. Cortisol is the stress hormone.

What I want to show you here is a laboratory experiment where we brought women back into our clinical research center, and they had to give a speech in front of a panel of judges with white coats on telling them, "You need to speak faster. You're not clear." They had to do some mental calculation. It's a standardized psychological test. The women all reported being stressed by this experience. It was a stressful experience, and that's what it was meant to be. We obviously didn't impair their safety. What I want to show you is

that the women who had a long-term history of fatigue after breast cancer had a very impaired response of their cortisol – that flight-and-fright hormone was very suppressed – whereas the women who didn't have a history of fatigue associated with their cancer treatments had a very nice response, again suggesting that our ability to cope with everyday stresses may be more complicated, and our ability to do this kind of cognitive functioning may be difficult.

What I think I want to leave you with is that whether there is such an entity as chemo brain or mental pause is really uncertain. It's clear that women report and experience these problems. How much of that is related to the menopause and our endocrine therapies versus the toxicity of chemotherapy, I'm not sure. Clearly, when we were giving bone marrow transplant-level, very high doses, I think we were probably injuring some individuals with that. But we don't do that today. We need to have more studies.

This is a diagram to look at how women are functioning in terms of their mental function. They're exposed to cancer treatments; it could be a variety of treatments. They have changes in their own hormones that could be affecting how their brain is functioning. They could have depression, fatigue or anxiety, though – and that may also affect how sharp they feel. They may also have changes in the immune system that may be revved up and causing them to not think as well. Probably chemo brain is somewhere in between here. It may not necessarily always be related to something that we can see on a scan or a test.

In conclusion, cognitive complaints after cancer treatment are pretty common. We really don't know exactly what's causing them. Some of them could be related to problems with sleep, management of menopausal symptoms. Clearly, if we can take care of those problems, I think women will feel better and think more sharply, there may be other individual risk factors that may put them at risk for this. Much more research is necessary.

I want to show a couple more slides. ... I wanted to basically show you some data from a study that we did. I was probably one of the first people to do a study focused on younger women with breast cancer. This was about 600 women who were two to ten years out after their diagnosis. This is the distribution of their age. If we think about younger women with breast cancer, even if we take women younger than 50,



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relatively few of them are going to be less than 40. This is their age at diagnosis.

Psychological late effects of cancer are really common. Depression and sadness and depressed mood are pretty common, particularly when you're in the midst of treatment or if you're having life events – you're getting divorced or you're changing jobs or a lot of those other things. That happens to other women at that age group and throughout life, these kinds of issues, but it's magnified if you've had breast cancer. There are certainly concerns about your future and death, health worries, inability to make plans. Some women will feel grateful that this allowed them to do something else and to change what they were doing in their life, feeling competent, taking care of themselves, but then there's uncertainty and vulnerability.

I want to show you why I said I don't think there's excessive depression. We know this from our studies. We used other standardized scales for women who have been treated with breast cancer, comparing them to healthy women. This is a standardized quality of life instrument called the SF-36. It looks at physical functioning, role functioning, emotional functioning, social functioning, pain, energy and fatigue and general health perceptions. I wanted to say that there is a gradient.

The very youngest women, if you look at the women who were 25 to 34 when they were treated, have the most serious trajectory in terms of emotional issues – I don't want to deny this. But they're not much out of the normal range, which, for this particular scale, is up around here. I'll show you some other data. Here, for energy and fatigue, it's down about half a standard deviation below the mean. There is something very special and very difficult if you're in this very young age group, but women who are a little older don't have as much trouble. When we look at women over age 50, there really isn't much perturbation in their emotional functioning.

WOMAN:

What are those numbers on the left?

PATRICIA A. GANZ, MD:

That's a score. The scale goes from zero to 100. These are the average scores, and the score goes from zero to 100 on this particular questionnaire. For instance, for physical functioning, women actually score in a really high range. These are survivors who are two to ten years out, maybe an average of six years out.

WOMAN:

So 50 percent of women in red have the fatigue?

PATRICIA A. GANZ, MD:

No. Their score is down at 50. Average for a woman that age might be 63, so they're about 10 points below. I think if I show you the next slide, it's less complicated. This is a way to look at these younger women compared to the general population. I didn't want to get too technical. The average for the general population of women who are in this age group, younger than 50, is at this score of 50. If we look at the physical functioning by when you had your breast cancer diagnosed, everybody is just average with the general population.

We see that the youngest women, the youngest survivors, are doing a little bit better. The difference between 50 and 52 is not significant. If we look here at the emotional or mental health and mental well-being, we see that women who were 35 to 39, 40 to 44, 45 to 51 [years old] when they were diagnosed are hovering around this score of 50. You have to be down at 40 to be even considered doing poorly, so even the women who are at 45 on this particular scale who were 25 to 34 [years old] are not doing that badly and are not significantly different. This is just a way of looking at this compared to the population.

These are women who are having hot flashes, menopause symptoms, chemopause, and they're still rating their quality of life as being pretty good. We used otherwise standardized depression scales, and they scored very similar to women in the general population going to their doctors. It's not to say that the issues and the concerns that are emotional and psychological are not important and valid, but that they're within a range of normal for the general population.

WOMAN:

Would you consider that 25 to 34 part of maturity?

PATRICIA A. GANZ, MD:

Yes. I think if you took most 25- to 34-year-olds who are at that point in their lives, trying to figure out what they're going to do with their career, are they going to have a child, are they going to get married to this person they've been living with for five years – I mean, that's part of life. What we see is that mental health improves as we get older. There's nothing worse than getting cancer at age 30. You've been hit by a Mack truck. This is not

when it's supposed to happen, so I feel great empathy. I have to tell you, coming here to this meeting yesterday and seeing so many young women was very hard on me. I'm a doctor, and I've been doing this for a long time, so I'm very sensitive and aware of what you've gone through. I can't live it with you, but I've lived it through my patients.

I wanted to say that there's not an excess of depression. You are going to have depressed and sad days. Some of you may be truly depressed and need medications, but you might have been that way anyway if you didn't have the cancer. That's the point I was trying to make. We can't blame you if you didn't do this and that and the other because there has been no evidence that getting control of your emotions is going to improve your survival. It will make you feel better; that's for sure. But there's nothing that will show that it improves your survival.

I want to point out here, again, what I've said here. The negative things are uncertainty about the future. We have more information today. All of you are on the Internet. All of you know your path[ology] reports. All of you have done Adjuvant Online. You know the hard statistics. That didn't happen 20 or 30 years ago. Because of the baby boom, we have more people who are younger who have gotten breast cancer. There are certainly negative things, but you have a lot more control. You are empowered, and you can do a lot to get control of your lives and hopefully improve your [chances] of never having a recurrence.

Now I'll take questions. (Applause)

WOMAN:

In the general population, hasn't stress been associated with depression? And haven't there been studies that have shown that people in stressful work situations, that's linked to depression? And wouldn't you consider cancer and the treatment for cancer as being stressful and therefore potentially leading [inaudible]?

PATRICIA A. GANZ, MD:

A couple of things: There have been some nice longitudinal studies, and there's one that just came out, again in JNCI. This is in the Netherlands, where they had population-based surveys of women who were coming in for mammographic screening, looking at stress and other features of their life. Then some of them got cancer. They went back to the questionnaires. The women who had more stress in their life didn't get cancer at a higher rate.



We also do not have any evidence that any of the treatments that we give for breast cancer lead to – okay, I want to be careful about this. We do have evidence now from some data that there may be changes in inflammatory markers that may lead the immune system to be dysregulated and turned on and overactive. Some of the data that I showed you about fatigue may do that, but we think many of these individuals are predisposed – they already have changes in their immune system before they ever get the cancer, and this is just another insult. It's not necessarily the cancer treatment that does this, but it's kind of the soil in which this occurs.

If the cancer treatments were causing you to be stressed and then led to a worse outcome, we wouldn't see the benefits and gains that we've seen in survival from breast cancer, which have literally marched through premenopausal women and are now being delivered in postmenopausal women.

Again, I want to say that the stress that you may have experienced right before your cancer diagnosis or after your treatment, if you remember that figure that I showed you about how the cancer started many, many years before – can you remember what kind of stress you were having 15 years ago?

WOMAN:

I've never had cancer; I had risk-reduction bilateral. But I don't think you addressed the question. What I said was stress in the workplace and stress in the general population has been linked to depression, and isn't it possible that the stress of a person having cancer and the stress of going through treatments, that stress itself could lead to depression irrespective of the treatment?

PATRICIA A. GANZ, MD:

Well, stress can lead to depression, but that we don't measure. . . . Again, the data that I just showed you, we do not find – there have been literally hundreds of studies that have not shown an excess of depressive symptoms or depression in women with breast cancer who have gone through treatment. I can just tell you, of the young patients I treat whose hormones get out of whack, they may get depressed because their hormones are very much affecting their brains.

WOMAN:

Even just from my own personal experience, and I know you don't want to hear about personal experience, but after having my ovaries out in May, I'm in complete and total menopause. I can have a number of, let's say, 10 hot flashes in the course of

a day. In a stressful situation such as a job interview, I will have hot flash after hot flash after hot flash, and I think stress does bring on those. And with hot flashes, one has anxiety attacks. Many women have suicidal thoughts. So I think hot flashes as a result of the treatments and as a result of chemo, all of these things can lead to depression.

PATRICIA A. GANZ, MD:

I absolutely agree with you, and I completely am sympathetic, and I have patients who are in exactly the same situation, but it is not the universe – that's what I'm trying to say. Everybody, just as I talked about how your breast tissue responds to your hormones in your body and how your bones respond, your brain and the brains of women like that are exquisitely sensitive to the hormones, and they need to be treated for those symptoms. But that is not the universe of women with breast cancer. Not everyone who has their ovaries out has that experience. It's just how your brain is wired. Not everyone has hot flashes. Most women at menopause do not have hot flashes.

WOMAN:

Can I ask a different question? I wanted to thank you for a very informative talk, and especially for explaining the whole influence of hormones on the risk of breast cancer developing. My question is: If a person is hormone receptor-negative and doesn't have a family history and doesn't have the BRCA genes – I don't know if there's data on this or not – what's the likelihood that the breast cancer was affected by hormones throughout the lifespan? Could the hormones still have played a role in the cancer developing even with the hormone negative?

PATRICIA A. GANZ, MD:

You're really asking what the natural history of a breast cancer is. Probably all breast tumors early in their life are estrogen receptor-positive, and some of them lose the receptor. A very good natural example is BRCA1-associated tumors. Most of them are triple negative. Most of them do not contain the estrogen receptor, but about 25 percent of them do, and we know that in BRCA1 carriers, if they have their ovaries removed before age 35, they gain the same benefit. Early in the life of the initiation of those very serious, high-risk patients, it's all estrogen receptor-positive, but the pathways, the mutations that are acquired along that 20-year trajectory, and what causes that cell to lose the hormone receptor is not well understood.

We now have five flavors of breast cancer: we have luminal A, luminal B, basal, normal breast type. I can't remember what the fifth type is. Oh, yes: triple-negative. Anyway, the point is that the pathogenesis and the development of what we see as the final product, which is the 2-centimeter breast tumor, started a long time ago and was initially estrogen receptor-positive. Without ovaries, you would never have gotten it, but it may not be necessary to sustain that cancer.

WOMAN:

Even if you don't have the gene mutations?

PATRICIA A. GANZ, MD:

Yes, because, again, those pathways are really similar.

WOMAN:

Could birth control pills 20 years ago have played a role? I know you said the low-dose ones now, but if you took it 20 years ago?

PATRICIA A. GANZ, MD:

We don't have good evidence. Again, because breast cancer in younger women is rare, we don't have it. Before 1975, the doses and therapies were really potent, and we think there were associations.

WOMAN:

What about the 1980s, were those low enough?

PATRICIA A. GANZ, MD:

Again, the general data is suggesting that. To try to figure out why you got it and why somebody else didn't, it's . . .

WOMAN:

We don't have enough answers.

PATRICIA A. GANZ, MD:

We don't have the data.

WOMAN:

All right, thank you.

WOMAN:

Mine I think is a simple yes/no answer. I'm sure you'll be delighted. (Laughter) When I read a slide talking about early menarche, I always think about me. I was a late bloomer, and my mother dragged me to the endocrinologist to find out what was wrong with me, and essentially I was 24 months behind where I really was. I wondered if there is any study or any research that's ever been done about late bloomers. When I graduated from high school, I was barely fitting in an A cup, and about 10 years later, I was a C. Is there anything with late bloomers in any respect . . .



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PATRICIA A. GANZ, MD:

Did you get put on any birth control pills or anything like that?

WOMAN:

Well, at age 16 I don't know what I was forced to do, but I was mad at my mother. That was the extent of that. (Laughter)

PATRICIA A. GANZ, MD:

I think where we have evidence is in less-developed parts of the world where women's nutrition isn't so good. Again, think about your daughters; if not yourselves, think about your daughters. Not growing up so fast and gaining weight leads to later onset of menstrual periods, which is a good thing by and large. I don't know about your unique situation. We can talk about it afterward.

WOMAN:

No studies out there, though? Nothing that you know of focused on late bloomers?

PATRICIA A. GANZ, MD:

Nothing that I know about.

WOMAN:

Just curious.

PATRICIA A. GANZ, MD:

In general, it's not an issue, but there may be something unique in your situation.

WOMAN:

I had a question about AIs. You had mentioned you want your estradiol level to be close to zero. I'm in a chemo-induced menopause and am taking different AIs for about the past 18 months, but what is the maximum level that you would want your estradiol to be?

PATRICIA A. GANZ, MD:

The AIs were designed for naturally postmenopausal women, not for women in your situation. In the naturally postmenopausal women – they were doing all of the original clinical trials – most of those women had levels of 11, 12, 15, like I showed you in that one study. The most potent one, which is letrozole, takes the levels down to around zero – hardly detectable. Some of them take it down to one or three. In a postmenopausal woman where we usually give the AIs, we don't want there to be any estrogen around, because her major source is coming from her fat tissue, not her ovaries. If your level is 15 to 20, you're taking a pill and it hasn't done its job.

WOMAN:

Well, I'm not that high.

WOMAN:

I wanted to know: What effect does the onset of chemo-induced menopause have on our bone health? Are there recommendations of ways that we can counteract bone density?

PATRICIA A. GANZ, MD:

That's an excellent question. It is an important issue. I really feel that you are an investment in the future. You are all going to live a long time, and I hope that we're going to figure out ways to make you live a long time. Knowing your bone health and your bone score – just like people learn their cholesterol number, you should know what your bone density is. Bone densities are calibrated against that of an average 35-year-old woman, so if you're less than 35 and you don't have the average bone density of 35, there are some issues there.

What happens is, when you go into an acute menopause or even a transient menopause with the chemotherapy, you actually have an abrupt loss of bone density, and then it stabilizes over the next couple of years. Particularly if you go on tamoxifen, it will help with [the loss of bone density]. I do routine bone densities, just as a baseline on all of my patients like you, so we know where you[r bones] are. Close to when we finish your chemotherapy, there's not such a dramatic change [in your bone density] that a few months doesn't make a difference. So, you know where you are in terms of your spine and your hip.

Again, vitamin D, calcium and exercise are all very important for everyone for bone health maintenance. We would only start some of those more intensive therapies with bisphosphonates if you were down to around minus 2. If you're on tamoxifen, it's going to help you and help manage your bones.

WOMAN:

My thing is: What are the effects of chemo on normal lab values, meaning CBC, ANAs, even the menopause? The second part of that is: How would someone like myself – treated with chemo and had stopped menstruation, sort of because of chemotherapy – how would I mark menopause with the laboratory testing?

PATRICIA A. GANZ, MD:

That came up in another session: How do you know when you're really ...

WOMAN:

But tied to that, the normal laboratory values, I get a lot of things blamed on, "This value was off because you had chemo." You can't diagnose anything that way.

PATRICIA A. GANZ, MD:

Normal chemistries – liver tests, all that – shouldn't be abnormal. I don't know what your chemotherapy was, but very few residual effects should be there. If you had a blood transfusion, obviously there could be some liver enzyme changes, hepatitis risk, things like that. Other than that, some patients will have low white counts. We sometimes see low platelet counts. It depends on how intensively you were treated. Rarely, anemia is a problem, but not liver test abnormalities. If women gain weight, they can have liver test abnormalities. Obesity, weight gain can lead to fatty liver and liver test abnormalities.

The other question was: When do you know when you're really menopausal? If you're still having occasional bleeds, you're not menopausal. We can't tell you when it's going to be, but it would be exactly the same for a woman I might be seeing in my high-risk clinic for who I'm trying to decide whether she'll tolerate tamoxifen, because she's near 50 and she's going to have a lot of hot flashes. It's really, really hard even for those women to know when it is going to end. You're just in the same boat with them, but you have experienced that probably ten years earlier.

WOMAN:

I have two questions, the first one being: What are your thoughts of bioidentical hormone replacement therapy in patients who have ER positive breast cancer? The second one I want to ask is: Has there been any research or information about risk factor for breast cancer with in vitro fertilization, since there's hyperstimulation of the ovaries?

PATRICIA A. GANZ, MD:

Two excellent questions. The bioidentical hormones are marketed and purported to be safer, but if they control your hot flashes, they're doing exactly the same thing as any other hormone you would take. They are no more or less safe. If you do a blood level on yourself, you'll have an estradiol level that will be appropriate for the management of your symptoms. I just saw somebody yesterday in my high-risk clinic who had atypical hyperplasia diagnosed on a biopsy, and she was taking bioidentical hormones for about a four- or five-



year period in her perimenopause. She was 51. Her estradiol is running around 30.

As I've told you – she's really now postmenopausal – 30 is high for postmenopause. It should be about 15, 20 at most. It doesn't matter if it's estradiol, whatever it is, if it's getting to a receptor in your brain so you're not getting a hot flash, it's working just like estrogen at the cellular level to cause cells to grow and divide.

WOMAN:

What about the creams for vaginal dryness?

PATRICIA A. GANZ, MD:

I would not use a cream. They get absorbed and get into the bloodstream. I would use Vagifem or the Estring, because they do not. Vagifem and Estring are FDA approved for women with a uterus. The reason progesterone had to be combined with – but, estrogen cream, if you give it to somebody with a uterus, she can have vaginal stimulation because you get pretty high levels with those ...

WOMAN:

What if you've had a hysterectomy?

PATRICIA A. GANZ, MD:

If you've had a hysterectomy, it's different. But, again, I would try to use the lowest dose possible. The vaginal ring, the Estring, and Vagifem don't get your levels up much above 20. I've seen some levels reported for the Vagifem of 30, 35. It's in the bloodstream. It's going everywhere in your body, so you just want to use the least bit. The problem with the creams is they get erratically absorbed and you may have high levels. I took care of a woman who had breast cancer diagnosed after having used just vaginal estrogen, Estrace or Premarin cream, for 20 or 30 years. I checked her estrogen level when her breast cancer was diagnosed. It was 75. It was getting absorbed into her bloodstream. You just need to be very cautious and use everything in the lowest minimal dose possible. Your other question ...

WOMAN:

IVF ...

PATRICIA A. GANZ, MD:

Oh, IVF, yes. That's an excellent question. Some epidemiologists have tried to look at this. The last information I saw was that there did not seem to be an association with the development of breast cancer. I will tell you where I would like to weigh in on this: Most women who are getting IVF are usually in their late 30s or early 40s.

They've tried to get pregnant in one way or another. As I showed you in that slide, it takes ten to 15 years to get to get a cancer. If you have IVF, or if you take hormone replacement therapy at menopause, you haven't caused that cancer. It's sitting there in the breast. It's perking its way along, but you may have accelerated its presentation by the high hormone levels, just like pregnancy does.

A woman who develops breast cancer during pregnancy, the pregnancy did not cause the cancer. Do not feel guilty for causing your cancer if it was diagnosed when you were pregnant. The precancerous and early cancer cells were there. You had something that wasn't appreciated, and the high hormone levels of the pregnancy made it clinically apparent. There should be no guilt associated with this, but it certainly could be related to the manifestations of the disease. There haven't been really conclusive studies on this, but understanding the hormones IOI gives you a picture.

WOMAN:

I have one small and one bigger question. My small question is: Are leg cramps and foot cramps associated with menopause, or am I insane? (Laughter)

PATRICIA A. GANZ, MD:

You know what? I didn't think they were until I did the STAR trial to look at raloxifene and tamoxifen. It turned out that both of those drugs cause it. Being now postmenopausal and never having had a leg cramp before in my life, I have had a few, and I think they're related.

WOMAN:

My second question is related. I learned a lot from your talk, but I would like to hear more about managing some of these symptoms. I was hoping to come away with something that would help me improve my quality of life with leg cramps.

PATRICIA A. GANZ, MD:

In terms of management, as I suggested, you need to get to a practitioner who is going to attend to all of those symptoms. We did a randomized trial several years ago where we had a nurse practitioner-driven intervention where the nurse basically assessed sexual functioning, vaginal dryness, hot flashes and sweats, and we used these various drugs and strategies in a systematic way, and if one wasn't working, we moved on to the other.

WOMAN:

Where do we find ...

PATRICIA A. GANZ, MD:

Where do you live?

WOMAN:

Massachusetts.

PATRICIA A. GANZ, MD:

What city?

WOMAN:

Littleton.

PATRICIA A. GANZ, MD:

It may be going off to the [Dana-Farber Cancer Institute in Boston, Massachusetts] for a consultation with some people ...

WOMAN:

But with Beth Israel [Deaconess Medical Center] there, so I have a ...

PATRICIA A. GANZ, MD:

I'm just saying, there should be someone – we will get you in touch with someone. In my place, that's what I do. I know a lot of other doctors in the community who do it. If you can get to an area where they're seeing and managing a lot of patients with this – these are very common things, and you have to just go through all the strategies. It's not a one-size-fits-all solution.

WOMAN:

You said to relieve the adverse effects you might put someone on hormone replacement for a short time. I was wondering if the person, I don't know who this person might be, had an oophorectomy and is on an AI and chose to deal with symptoms for the five years, then at that time can they take a low-dose hormone replacement to relieve the menopause symptoms and go back on tamoxifen just for quality?

PATRICIA A. GANZ, MD:

The therapy you're describing is quite irregular, so anything that anybody would design for you would be nonconventional.

WOMAN:

Because of the SOFT trial, that's what I'm doing ...

PATRICIA A. GANZ, MD:

That's what you're doing.

WOMAN:

I'm doing the SOFT trial and I'm on ...



PATRICIA A. GANZ, MD:

I'm sorry. I apologize. If you were doing it not on the trial, it would be an issue. There will probably be decisions made in the trial as to what you can and cannot do. I would really wait, since you are in a trial . . .

WOMAN:

Yes, I'm planning on just doing this for the five years, but I wondered, at the end, why couldn't I – for vaginal dryness or something – take a low-dose hormone and then take tamoxifen for an extended period to combat the estrogen?

PATRICIA A. GANZ, MD:

It's very hard to comment because I don't know what your risk is, how big your tumor was and all those kinds of things. It's hard for me to tell you. Maybe we can talk about it afterward, and I can give you a personal opinion then.

WOMAN:

I have a question for patients who are on tamoxifen and also Zoladex.

PATRICIA A. GANZ, MD:

Are you also on the SOFT trial?

WOMAN:

No.

PATRICIA A. GANZ, MD:

Your doctor is treating you that way?

WOMAN:

Right, just tamoxifen and Zoladex. You mentioned earlier that tamoxifen counteracts bone loss. But for patients who are on those drugs and are still getting rapid bone loss, what can they do? And some of the drugs that are mentioned, like Fosamax and Zometa, what drugs are safer? And . . .

PATRICIA A. GANZ, MD:

It really depends. This is the kind of thing you would discuss with your internist who has a lot more experience treating postmenopausal women. There are a whole group of different drugs, some that need to be given less frequently than others. The one that's been more associated with jaw necrosis is Zometa, so I would probably avoid that, but all of them probably work pretty much in the same way, and it's a matter of convenience how you want to take it.

WOMAN:

Did you say to avoid Zometa?

PATRICIA A. GANZ, MD:

I would probably not take Zometa, because that drug is the one that's been more associated with jaw necrosis.

WOMAN:

That's the one they recommended for me.

PATRICIA A. GANZ, MD:

Is that the oncologist or your internist?

WOMAN:

The oncologist.

WOMAN:

That's an endocrinologist.

PATRICIA A. GANZ, MD:

I mean, I think you need to basically go to somebody who every day is treating osteoporosis. Your oncologist is usually not the best person. In my own practice, I defer to the primary care doctor.

WOMAN:

The endocrinologist right now is putting me on the vitamin D test, where I've been given a high dose of vitamin D to see if that would increase the calcium absorption. I would be getting . . .

PATRICIA A. GANZ, MD:

How bad is your bone density?

WOMAN:

Five percent bone loss.

PATRICIA A. GANZ, MD:

Only 5 percent bone loss?

WOMAN:

Right.

PATRICIA A. GANZ, MD:

I wouldn't do anything. We all lose 1 percent per year. That's what we're all losing. How long have you been on treatment?

WOMAN:

I'm on hormonal and about a year-and-a-half out for the Zoladex, and about two years for the tamoxifen.

PATRICIA A. GANZ, MD:

I have to tell you that the bone density tests are not reliable if you do them more frequently than every 18 months to two years. There's an error in measurement. We don't make any changes in somebody's therapy or start them on something until they meet criteria for bone loss down to between 1.5 and minus 2.0 in terms of the standard deviation T-scores. You may be just looking at measurement error.

WOMAN:

Thank you.

WOMAN:

I'm a DES daughter, and I also had breast cancer. I'm wondering if there is a correlation between DES [diethylstilbestrol, a synthetic estrogen] exposure in utero and breast cancer.

PATRICIA A. GANZ, MD:

There is. You're all just getting old enough so that that's happening. Yes, there absolutely is.

WOMAN:

Are there studies that I can find, any access or any database?

PATRICIA A. GANZ, MD:

If you send me an e-mail – I'll give you my card – I'll try to find something. The DES mothers were the first to get breast cancer, and the DES daughters obviously had vaginal and other gynecological problems, and they are now old enough that they are getting breast cancer.

WOMAN:

Okay, so there is a link.

PATRICIA A. GANZ, MD:

Yes.

WOMAN:

Thank you.

WOMAN:

If you have chemo-induced menopause, when do the hot flashes stop?

PATRICIA A. GANZ, MD:

It's quite variable. Referring you to what happens generally, I would say 10 percent to 15 percent of women who go through natural menopause in their early 50s have persistent hot flashes and are troubled for a long time. The majority have two to three years of symptoms. Sometimes it's before they actually stop menstruating, and sometimes it's after. I can only say that time heals in this situation. Again, it could be complicated if you're on tamoxifen while you're experiencing this. That can exacerbate it, and it might not go away until you stop the tamoxifen.

But if it's just because you had chemotherapy and went into menopause, it's an average of three to five years. There are even 60-year-old women who will still have a twinge of a hot flash ten years after they stopped menstruating. It's not over 'til it's over, in a sense. We are dynamic human beings experiencing what's going on in our bodies. The mind and the body, in terms of these hormones,



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are very interconnected. Hopefully it's getting better for you. Most of my patients tell me that first year is the worst one, and then the second and the third are a bit better.

WOMAN:

What about surgical menopause?

PATRICIA A. GANZ, MD:

Patients who have this, it's really intense up front. A lot of them are kind of better in a year. It's very compressed. When we talk about chemopause being an acceleration of that ten-year perimenopause into a two- or three-year period of time in the surgical, it's even sometimes within a year or two that the drama kind of completes itself.

WOMAN:

I want to address bone health again. Calcium pills and vitamin D has been the major staple for a lot of American women. With the intake, is there a study supporting that there are decreases in osteoporosis in the United States?

PATRICIA A. GANZ, MD:

I think you're in a different situation, because mostly they have been done in postmenopausal women, older, over age 50.

WOMAN:

If they take vitamin D with calcium, shouldn't that halt their problem? And if it's not, like, such a question: Is there validity in taking calcium with vitamin D? I know you don't want personal examples. I had breast cancer when I was 27. I danced like a maniac, five days a week dancing, high-impact aerobics. I'm not talking about aerobics classes; just dancing. And I took tamoxifen.

At the end of my six years of tamoxifen, the cancer recurred two years afterward, and I had a DEXA [bone density] scan at that time. They said I have osteopenia. I was very surprised. I mean, against all the tamoxifen, strengthening of the bone, high-impact aerobics – it wouldn't help me. Then, eventually I have to take Zometa. I stopped taking . . .

PATRICIA A. GANZ, MD:

[Inaudible] calcium.

WOMAN:

No, I stopped. I take vegetables, green, dark-leafed vegetables. I've done some research, and there is some study talking about osteoporosis not being the result of lack of calcium. It's acidity of the body. The body is extracting the calcium to counter

the acidity. I start to recall maybe that's why I was still having bone problems before. There are studies showing that it's the lack of magnesium and a compound of silicone.

PATRICIA A. GANZ, MD:

There are a couple of things that I think are important in your situation. Without knowing where your baseline bone density was before you ever got your breast cancer treatment, it's hard to know what your bone mass was. Even though you are a vigorous dancer and everything like that, your diet may not have been rich in calcium. I don't know what part of the world you grew up in, if you had a lot of dairy products when you were growing up.

WOMAN:

Yes, I'm a first generation in the United States.

PATRICIA A. GANZ, MD:

The point is that many women diet and do a lot of other things that don't maintain their intake, so that they come to adult life with a lower bone mass than the average woman. If you had a low bone mass to begin with and then took tamoxifen for several years – as I said, you lose bone mass during the first few years with tamoxifen, and then it restabilizes. With the information you have seven or eight years out, I don't know what the history was. In fact, had you not been taking calcium, your bone mass may have been even lower. We can't answer it from your own situation.

Calcium is necessary to build bones. You don't have to take it in supplements if you eat enough products that have calcium. Nobody is saying you have to take supplements. If you eat foods that are rich in calcium and vitamin D and a normal diet and are physically active, most people will have adequate bone health. But there are also genetic components. People from northern Europe and even some people from Asia may have lower bone mass to begin with, so even calibrating the bone density machine, it may not be calibrated for your ethnicity.

WOMAN:

In America, so many women are taking calcium pills and vitamin D, but all of them are still having bone problems.

PATRICIA A. GANZ, MD:

They may be worse off. They may be worse off if they didn't take it. It doesn't actually treat osteoporosis. That's what we learned from the Women's Health Initiative Study.

WOMAN:

You had a slide that gave several ways to manage menopausal symptoms – hot flashes, vaginal dryness. I have a lot more of a problem with the joint pain, the stiffness. Do you have anything that goes along to help with those symptoms?

PATRICIA A. GANZ, MD:

That's from an AI, or is that just from going through menopause?

WOMAN:

Probably all the chemo that I've been on, and then oophorectomy.

PATRICIA A. GANZ, MD:

This is one of those uncovered symptoms that we haven't really addressed. If you remember, back in my early slides I showed you how joint pains in healthy women go up with age. You are experiencing what a woman in her 50s and 60s would possibly be experiencing, but it's at the wrong time. You probably would have developed these same symptoms when you would have gone through menopause normally. But you, unfortunately in a body that's much younger, are experiencing these.

I feel that we need to figure this out for the general population of women, but maybe the breast cancer survivors like you with the AIs, with the premature menopause, will be our laboratory to be able to try to find some treatments. Right now, there isn't anything. People are experimenting and beginning to study this. I would look out for clinical trials for survivors, because I think all of you who have these kinds of symptoms have survivorship concerns, and there is a big move afoot to pay much more attention to these concerns. Think about where a woman in her 50s and 60s would be. If you're in your 30s or 40s, you could be experiencing those same symptoms transformed at a younger age.

MARCIA STEIN:

I want to thank everybody for coming. It's been a great talk. I know Dr. Ganz is available after the talk. Everybody have a good time at the dinner tonight and the dance. Bye. (Applause)