

Keeping Your Bones Strong During and After Cancer Treatment

Dr. Joy Y. Wu of Stanford University School of Medicine

National Webinar Transcript

February 15, 2022

Presented by:



**SHARSHERET**

The Jewish Breast & Ovarian Cancer Community

This program was made possible with support from

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Oncology

## Keeping Your Bones Strong with Dr. Joy Wu

Melissa Rosen:

... much. My name is Melissa Rosen and I am the Director of Training and Education at Sharsheret. I want to thank everyone for being with us today for an important conversation about bone health and cancer. Tonight, we will be learning from Dr. Joy Wu about how to protect your bones during and after cancer treatment. And we are grateful for tonight's webinar sponsor, Amgen. It's thanks to their support that we will be able to provide this series of three webinars on bone health. As we prepare to begin tonight, let me just go over a few housekeeping items. Today's webinar is being recorded and posted on Sharsheret's website along with the transcript. As usual, participants' faces and names will not be included in the recording. But if you would like to remain private tonight, you can turn off your video and rename yourself, or you can call into the webinar. Instructions on how to do that are being posted in the chat box now.

Melissa Rosen:

You may have noted that you were muted upon entering the Zoom room. Please stay muted throughout the program. If you have any questions, you're encouraged to type them into the chat box, and we will answer them during the Q and A session tonight. We recommend that you keep your screen on speaker view. This will enable you to see the doctor's presentation. And you can find this option in the upper right hand corner of your screen. As we move into the webinar itself, I just want to remind you that Sharsheret is a national not for profit cancer support and education organization, and does not provide any medical advice or perform any medical procedures. The information provided by Sharsheret is not a substitute for medical advice or treatment for specific medical conditions. You should not use tonight's information to diagnose or treat a health problem. If you have any questions specific to your medical care, you should be speaking to your medical provider. Always seek the advice of a physician or qualified healthcare provider with any questions you may have regarding your specific medical condition.

Melissa Rosen:

As I mentioned, today's webinar is just the first of a series of three webinars on bone health. Over the course of three webinars, we will provide an overview of what impacts bone health, how cancer treatment affects your bones and what you can do to keep your bones healthy and strong before, during and after treatment. Forthcoming webinars will focus on bone health and nutrition, and bone health and fitness. Our follow up email with the recording and transcript from today's program will also include information, two resources that will help you with bone health. And if you'd like to learn more about osteoporosis and cancer, Sharsheret has a great survivorship kit called Thriving Again that comes with an exercise band, as well as additional information on bone health and osteoporosis. If you have further questions, our social workers are always here to provide you with additional resources. In fact, if you've already received a Thriving Again kit but would like more information on bone health, you can absolutely just request that as well.

Melissa Rosen:

And now tonight, this evening, we are so honored to be joined by Dr. Joy Wu. Dr. Wu is a tenured Associate Professor of Medicine, endocrinology specifically, and Vice Chair of Basic and Translational Science in the Department of Medicine at Stanford University School of Medicine. She is an internationally recognized leader in bone health and the treatment of osteoporosis in patients with cancer. She directs a basic and translational research program that focuses on skeletal development, stem cell therapies for bone, and breast cancer bone metastases. She has served on clinical guideline

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committees on bone health and cancer for the Endocrine Society, the American Society of Clinical Oncology, and the American Society for Transplantation and Cellular Therapy.

Melissa Rosen:

Dr. Wu earned her MD and PhD degrees at Duke University followed by clinical training in endocrinology at Harvard Medical School and joined Stanford in 2012. And if all that wasn't enough, she is also the recipient of the NIH Director's New Innovator Award and her research has been funded by the National Institutes of Health, NIH, the Mary Kay Foundation, and the Department of Defense. Dr. Wu is currently an ambassador for the American Society for Bone and Mineral Research and a member of the board of directors of the Endocrine Society. You can see why we are so honored to have her here with us this evening. Dr. Wu, thank you so much. And the screen is yours.

Dr. Joy Wu:

Thank you, Melissa, for that very kind introduction. And thank you to Sharsheret for this opportunity. It's really a privilege to be here and to speak with you all tonight. Let me just share my screen. All right. And does that look okay?

Melissa Rosen:

Perfect.

Dr. Joy Wu:

Wonderful. Thank you so much. All right. So it's really a pleasure to be here. This is a topic that is deeply meaningful to me. And I'm pleased to have this opportunity to talk about keeping your bones strong during and after cancer treatment. So whenever you listen to a medical professional, you should ask whether there are any conflicts of interest. Given that Amgen is a sponsor of this series, I want to state upfront that I receive no personal compensation nor research funding from Amgen and Amgen had no influence over the contents of this presentation. Like many researchers, I do receive federal research funding from the National Institutes of Health.

Dr. Joy Wu:

So the topics that I'd like to cover tonight include why we're even talking about bone health importance, the effects of cancer treatment on your bones, how you can optimize your bone health through diet and exercise, and when lifestyle interventions are not enough, how we can use medications to improve our bone strength. As I mentioned, this is a topic that's very personally meaningful to me. It's something that I work on in the clinic. My clinical practice specializes in women with breast cancer and their bone health. And I'm also a research scientist. I run a lab in which we study how to prevent breast cancer bone metastases. I'm sorry-

Melissa Rosen:

I'm going to interrupt for one second. And can everybody please ensure that they're muted. Thank you so much.

Dr. Joy Wu:

Thank you very much. So as a research scientist, it's something that we study in the lab, specifically how we might prevent metastases of breast cancer from spreading to the bone. But I have a third

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perspective, which is like many of you, I'm also a breast cancer survivor myself. So this is an area about which I'm deeply involved and interested. Let me start with the take-home messages that I hope that you'll remember from this talk. Number one is that cancer treatment can have effects on your bone health. Fractures that are related to osteoporosis, which is a disease of bone fragility, are serious but preventable. Your risk of a fracture depends on many factors, which we'll discuss in detail. Lifestyle changes can certainly slow, but usually cannot reverse bone loss. And when used properly, osteoporosis medications are extremely safe and effective.

Dr. Joy Wu:

With that, let's start with the definition of osteoporosis. It literally means porous bone. And it refers to a decrease in bone mass that leads to an increase in fragility and increase in your chance of having a fracture. And this is just an artistic rendering of what a bone would look like under a microscope. You can see normally there's quite thick connections. And as we get older or develop osteoporosis, this can become quite thin. Osteoporosis is extremely common. It's estimated that half of all women over the age of 50 will experience a fracture in their lifetime due to osteoporosis, compare that with a risk of breast cancer in the general population of about 12%. Men are also at risk for osteoporosis. About a quarter or 20% of men themselves will experience a fracture. And that's somewhat similar to the rate of prostate cancer among men.

Dr. Joy Wu:

In the US every day, there are over 5,000 fractures that occur due to osteoporosis. This is a fracture cast (pictured) that is travels around the country to make the point that there are many fractures that occur every day. Here's a person in the background, so you can see how tall this cast is. That turns out to two million fractures per year. So this is a serious public health issue. It affects at least 10 million Americans, the majority of whom are women. As I've mentioned, there are two million fractures per year. And the costs are now probably over \$20 billion per year. When we talk about fractures that are due to osteoporosis, the most common single site is the spine or vertebral fractures. Next most common are wrist fractures. For instance, when somebody trips and falls and puts out the arm to break their fall, they can fracture their wrist. Perhaps the most dreaded complications are hip fractures. These are very serious and can lead to a loss of independence and ability to walk. And then the other 40% affect the pelvis and other bones.

Dr. Joy Wu:

Why are we talking about osteoporosis tonight? Because it's very common among patients who have been treated for breast and ovarian cancer. And that's because women who are treated for these cancers have multiple risk factors that can lead to bone loss. Chemotherapy itself, while very beneficial for reducing the cancer, treating the cancer, can have toxic effects on the bones. For premenopausal women who are being treated with chemotherapy, it's quite common that they can be forced into a premature or early menopause, and this is a condition that's associated with bone loss. We'll talk in more detail on the next few slides about endocrine therapy, which is a particular way to treat breast and ovarian cancer. And then radiation therapy is also quite common in treatment modalities for these cancers and radiation can have toxic effects on the bone.

Dr. Joy Wu:

This is just a graph that shows the number of fractures per 10,000 people-years. So for instance, 1,000 patients followed over 10 years. In light gray are survivors of breast cancer and in dark gray are the

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comparison general population rates. And you can see that the fracture rates are much higher among patients with history of cancer. So let's talk for a moment about endocrine therapy for cancer. About 80% of breast cancers express the receptor for hormones, including estrogen and progesterone. In our bodies, estrogens are made in the ovaries for premenopausal women. And then in the adrenal glands, which sit here on top of the kidneys for women after menopause. The fact that cancers express estrogen receptors means that we can take advantage of this as a treatment approach. And there are a number of therapeutic approaches that we can use.

Dr. Joy Wu:

So the first are selective estrogen receptor modulators, most commonly, tamoxifen. This is used to treat many women to prevent recurrence of breast cancer. Aromatase inhibitors are a class of medications that try to block the estrogens that are made from the adrenal glands. And you might recognize them as anastrozole, exemestane, or letrozole. These are used in postmenopausal women. In women who are premenopausal who need aromatase inhibitors, they also must be treated with ovarian suppression because premenopausal women make a lot of estrogen from the ovaries. And to do that, we often use GnRH agonists like goserelin or leuprolide that suppress production of that. And finally, there are estrogen blockers called fulvestrant. Currently they are used for metastatic disease only.

Dr. Joy Wu:

So these endocrine therapies are very effective at treating breast cancer and preventing recurrence, but they can be tough on the bones. And to give you an idea of how much effect they can have, shown here on the left are the normal rates of bone loss for men and women who are healthy. So a normal man is losing about half a percent of the amount of bone every year. Women lose a little bit more. After menopause, they lose on average 1% per year. That's one of the reasons women have higher rates of osteoporosis. In healthy women, the fastest rate of bone loss happens right around the time of menopause. So the couple of years surrounding the time when your period stop. And in healthy women, again, that sort of peaks at about 2% per year.

Dr. Joy Wu:

So this is about the fastest rate that we ever see healthy women losing bone is in the years right around menopause. Now, if you look in postmenopausal women being treated for cancer on aromatase inhibitors, that rate is a little bit higher. So it's about 2.6% per year. And over on the right, if you look at premenopausal women who are being treated with both aromatase inhibitors and ovarian suppression, that rate is almost three times, more than three times higher than normal. That's 7% per year. And similar numbers for women who have chemotherapy induced early menopause or premature menopause. So you can see these are rates of bone loss that are much higher than normal.

Dr. Joy Wu:

All right. So let's talk about the risk factors for bone loss. The greatest is probably age. As we age, the amount of bone that we have decreases, and this can lead to increased fragility and fracture risk. If you've had a previous fracture, that's a warning sign. So for instance, if you have in the past slipped and tripped and put out your arm and fractured a wrist, then that puts you at higher risk for having more fractures in the future. Some medications like glucocorticoids also known as steroids can cause bone loss. Your family history, just like it matters for breast cancer matters for osteoporosis, especially if you've had a parent who has had a hip fracture. In the medical field, we often tell patients that being overweight is a risk for diseases. But for osteoporosis, it's actually the opposite. Being too thin, having

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low body weight is a risk here. Smoking, excessive alcohol intake, which is defined as more than two drinks per day for women, more than three drinks per day for men are also associated with bone loss. And some diseases like inflammatory conditions, such as rheumatoid arthritis and other causes of osteoporosis.

Dr. Joy Wu:

So to figure out if you are at risk for osteoporosis, the most commonly performed test is what we call a bone density scan. And this is one of our machines here at Stanford Hospital with the technician. So you can see you lie down on the bed. This is sort of an x-ray like beam that takes pictures through the spine and the hip. It takes about 10 minutes. It doesn't hurt. And it's really a very tiny amount of radiation. And we get information usually about your bone density at the hip and at the spine. And it gives us information comparing your bone density to the average 30 year old woman. And we use 30 year old women because that's really when bone density is at its peak. So we compare against reference database information from 30 year old young adult women.

Dr. Joy Wu:

And I'll walk you through this slide. So what the bone density report gives you is what we call a T score. So this is the standard deviation compared to a young 30 year old woman. So for instance, if it's minus one, that means that your bone density is one standard deviation lower than that of a 30 year old woman. And down to minus one is normal bone density. Between minus one and minus 2.5 is considered intermediate, a term that we often call osteopenia. And then osteoporosis is defined by the World Health Organization as a bone density T score of minus 2.5 or lower. Now I mentioned that age is also an important factor. So the point of this slide is to try to bring that home. So this is a woman who weighs 150 pounds, five foot six inches, and calculating her risk of fracture, specifically a hip fracture over the next 10 years.

Dr. Joy Wu:

Hip fractures, as I mentioned, are quite devastating. Less than half of people who have a hip fracture ever walk again. So we have a pretty low threshold for recommending treatment. And that threshold is if you have a 3% risk over the next 10 years, then we will recommend treatment. That's what this dotted line is across the graph. And what I've then shown you is for every age between 55 and 80 at five year increments, what your risk looks like. So a 65 year old woman who has osteoporosis, that means a T score of minus 2.5 is right at the threshold. So for a 65 year old woman with a T score of minus 2.5, I would generally recommend treatment or medication for osteoporosis. If you are younger, then you're a little bit protected. And so you might not reach that risk until your T score is as low as minus 2.8.

Dr. Joy Wu:

So for younger women than 65, sometimes even though their T score meets criteria for osteoporosis, I might say to them, we can wait a few years before we start medication. Let's try to work on lifestyle. But the converse is also true. As you get older, your bone density doesn't need to be as low for you to have the same risk. So for example, at the extreme here, we have an 80 year old woman. Even with a near normal bone density of a T score minus 1.2, so that's really borderline osteopenia, almost normal, she would still meet the recommendations for treatment. And again, that's because age is an independent risk factor for fracture.

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Dr. Joy Wu:

The other thing that affects your risk of having a fracture or a broken bone is the number of risk factors that you have. So remember on an earlier slide, I talked about certain risk factors, including age, bone density, but also whether you've had a previous fracture, whether your parent has had a hip fracture, whether you're a current smoker or user of tobacco, whether you're being treated with steroids also called glucocorticoids, whether you have inflammatory conditions such as rheumatoid arthritis, or whether you have excessive alcohol intake. So again, here is a woman at age 65. Same weight, 150 pounds. Same height, five foot six inches. Again, I've drawn the line at roughly 3%, which is the threshold at which we recommend treatment. And you can see that the larger the number of risk factors that this woman has, the more likely she is to be above that threshold.

Dr. Joy Wu:

All right. So who should have a bone density test? Let's start with the general population recommendations. This is borrowed from the American Society of Bone and Mineral Research to which I belong. So for the general population, bone density scans are recommended for women over the age of 65, men over the age of maybe 70 to 75. If you're over the age of 50 and you have significant risk factors like the ones we talked about, then you can also be recommended to have a bone density test. If you've had a fracture that was what we call low-trauma, meaning you just tripped and fell on the sidewalk, or you had a spontaneous spine fracture, those individuals also should have a bone density test if they've had a fracture as an adult. And then anyone who has either a disease like rheumatoid arthritis, or is taking a medication such as glucocorticoids, that can be associated with bone loss.

Dr. Joy Wu:

Now for cancer treatment indications, the recommendations are that all postmenopausal women should be sent for a bone density test. Premenopausal women, so these are on average younger women who are being treated with ovarian suppression and an aromatase inhibitor should also be sent for a bone density test. And then there's some uncertainty in the field about whether premenopausal women who are being treated with tamoxifen should also be recommended. And the reason is that tamoxifen is not nearly as hard on the bones as ovarian suppression and aromatase inhibitor. So now let's talk about what we can all do to strengthen our bones and keep our bones healthy. This is from the Surgeon General's Report on Bone Health, and these are general recommendations. So number one is get enough calcium and vitamin D. And on the next slides, I'll talk about how you can do that. Be physically active. So we'll also talk about exercise and its role in keeping your bones strong.

Dr. Joy Wu:

Reduce your risk of falls. So this means things like being careful around the house. If you have throw rugs, making sure that they're sort of taped down, that they're not loose, that you don't have sort of a loose corner to trip on. Of course, keeping your stairs clear of anything you might trip over. And other things like for instance, having a nightlight in the bathroom so that when you get up in the middle of the night to go to the bathroom, that you don't trip over something and fall. Maintaining a healthy weight. So that means not too thin or not too overweight. Not smoking or stopping a tobacco use if you're a smoker. Limiting your alcohol use. And then finally, talking to your doctor about whether there are any medications that you're taking or any other medical conditions that you might have could be affecting your bones.

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Dr. Joy Wu:

All right. So let's talk about how much calcium you should be taking. So for women at risk of bone loss, so postmenopausal women or those who have osteopenia or osteoporosis, I generally recommend about 1000 to 1200 milligrams a day. This can be a combination of diet or supplements as long as it totals in this range. So dietary sources, the best sources of calcium in the diet are the dairy products. So milk, yogurt, cheese, those on average have close to 300 milligrams of calcium. So two to three servings a day would get you very close to this number. There's also calcium in other foods. You can find them for instance, in fortified orange juice, canned salmon, especially if it contains the bones, cottage cheese, even in green vegetables, there's some calcium. So these are great sources to get calcium. And if you can, you can try to add these all up to get 1200 milligrams a day.

Dr. Joy Wu:

Now, most adults who see me in my clinic don't have two or three servings of dairy. Most people have one maybe a day. So it can be hard to reach 1200 milligrams a day just by diet alone. And that's okay. Then you can take calcium supplements. The important thing to remember is you want to check the label for the elemental calcium amount, that's on the label. Again, you're looking for a total in the range of 1000 to 1200 milligrams a day. Also, keep in mind that your stomach really can't absorb more than about 500 milligrams at a time.

Dr. Joy Wu:

So if you're not someone who can get much calcium in the diet, for instance, if you're lactose intolerant or maybe on a vegan diet and you need to rely entirely on supplements, then you want to do two supplements at different times of the day. So maybe five to 600 milligrams at a time. If you are taking acid blocking medication, so these are things like the proton pump inhibitors, H2 blockers, then I recommend calcium citrate because it doesn't depend on acid to be absorbed. But otherwise calcium carbonate is a great source. And you'll find this on the shelf of your pharmacy over the counter, for instance, as Os-Cal or Tums or generic calcium carbonate.

Dr. Joy Wu:

The next thing we need is vitamin D. Vitamin D is important for helping our bodies to absorb the calcium from our diet. Again, for most individuals at risk of bone loss, I recommend 800 to 1000 international units a day. And there are different forms of vitamin D. There's vitamin D2, which is a plant-based supplement. Or vitamin D3, which is the same version that we produce ourselves in the skin in response to sunlight, or that we ingest from foods. All right. The next important lifestyle intervention for keeping bones healthy is physical activity or exercise. So the American Heart Association recommends for everybody that we should be active at least 150 minutes a week of moderate or 75 minutes of vigorous activity each week. I generally tell patients they should aim for 30 minutes a day. This can be any exercise that you enjoy. It can be walking. It can be running, swimming. The most important thing is to find something that you'll stick to.

Dr. Joy Wu:

So 30 minutes a day of activity. Two to three times a week, specifically for your bones, that should focus on strength training. And there are many ways to accomplish this. You can use free weights. You can use weight machines at the gym. You can buy resistance bands, anything that really challenges your muscles, two to three times a week. And the general principles are that you want to be working out all the major muscle groups, upper and lower body, and that it should be challenging. So the number



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doesn't matter, but it should be something that you're pushing yourself a little bit to always improve. Balance and flexibility are also important. Part of the reason adults fracture more as they get older is because their balance becomes impaired and they're more likely to fall. And so things like yoga, Pilates to maintain your balance and flexibility are also important. And the Bone Health and Osteoporosis Foundation does have some recommendations for patients that you can find on their website in terms of how to have a healthy exercise regimen.

Dr. Joy Wu:

All right. So for some people, if you have osteoporosis or if you're on an aromatase inhibitor and the amount of bone is going to be significantly impacted, all of the lifestyle, you can do everything right lifestyle-wise, and it's just not going to be enough to restore your bone back to the normal range. And so that's when we need to think about medications for treating osteoporosis. So when I see patients in my clinic, I tell them that the amount of bone is really a balance between the breakdown that occurs every day and new bone formation. So that means that our treatment strategies are to either prevent this breakdown or to try and promote bone formation. Let me start by saying that we have very little safety data about these bone forming medications for osteoporosis in breast cancer. So my colleagues and I generally don't recommend these. So for that reason, we're going to focus on the two most common kinds of medications for treating osteoporosis. And these are medications that prevent the breakdown of bone.

Dr. Joy Wu:

So here I've listed a table. It's got a lot of information, but I'll walk you through it. These are the commonly used medications for treating osteoporosis in cancer patients. First, we have a class of medications called bisphosphonates that are given by mouth. You may be familiar with them by their trade names from maybe commercials on TV or magazine ads. And these include Alendronate which is marketed as Fosamax, Risedronate which is Actonel, and Ibandronate which is Boniva. These are oral medications that are given once a week with the exception of Boniva, which is once a month. These are extremely safe and effective medication. Alendronate is my go-to medication for almost everybody. That's my first line, first choice. There are a few things that we do have to consider. These pills sometimes cause heartburn. So if you have a history of heartburn or gastroesophageal reflux disease, sometimes this can aggravate that and irritate your stomach or GI tract.

Dr. Joy Wu:

They have some limitations for people who have reduced kidney function. So if you have chronic kidney disease, we do have to be cautious. And then the bolded names are the ones who've been shown to prevent all kinds of fractures. And just a note that Boniva has not reached the same level of evidence as the other two. So again, my first line choice is usually Fosamax. For those who develop heartburn, or maybe for various reasons can't take weekly tablets, there's an intravenous version, Zoledronic acid marketed in the US as Reclast. This is an infusion, meaning that you have to have an IV line. But to counter that, the advantage is that it's only once a year. So although you need to go in and have an infusion done, it can be given once a year and it will really protect your skeleton for the duration.

Dr. Joy Wu:

So that means it's quite common. Convenient, sorry. It also like the oral tablets has some limitations in people who have kidney disease. And then because this is an infusion, some people do report that they notice a flu-like reaction in the day or so after they have the infusion. This can feel like a low-grade

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temperature, a little bit of aching in the muscles and joints. Right now, this is very similar to what people are reporting after their COVID vaccines. So hopefully, you've been vaccinated against COVID. You may have experienced similar reactions. That's what I hear from my patients who get Reclast as well. There's a second class of medication that has only one medication, and that's a monoclonal antibody against a protein called RANK ligand. The medication is Denosumab, marketed in the US as Prolia. This is an injection every six months. So it means you come into the clinic, you get a shot. You don't need an IV, it's not an infusion. You just get a shot. So it's very quick, but every six months.

Dr. Joy Wu:

It has some nice advantages. It does significantly increase your bone mineral density. And the other nice option is that it is an option for those who have chronic kidney disease, because again, the bisphosphonates are not always the first line. Some things to be aware of. It can't be stopped abruptly. So with the bisphosphonates, if you stopped or you missed a dose, you could just sort of pick back up, but Prolia cannot be stopped abruptly because this increase in bone density can be very rapidly lost. And so you have to come up with a management plan with your doctor to not stop it. And there's a little bit of concern that it may have some increased risk for infection in people with immune compromised. But generally all of these medications are very safe, very effective.

Dr. Joy Wu:

Now, I've been practicing medicine for more than 20 years. I've really heard it all. And again, this is my focus. So I really do nothing other than take care of patients who have bone loss and osteoporosis. And these are some of the common things that I hear when I bring up the possibility of medications. And many of you may have similar thoughts or concerns. So it's very common for me to hear from patients that they prefer natural remedies to taking medication, or no medication at all. That they're very sensitive. They've read that osteoporosis medications can be dangerous. Or that they have a close friend or family relative who has had this medication and some kind of unpleasant side effect. And I understand, I think we're all influenced by what we hear from those closest to us. So these are very common concerns. But I just want to emphasize. So when these medications are used properly, they can be extremely effective.

Dr. Joy Wu:

So let's talk about the risks and benefits of these medications. So this is a graph of the number of events per 100,000 patient-years. So again, for example, this could be 10,000 women followed for 10 years. And shown in gray here in the first three columns are the number of spine, wrist, and hip fractures that would occur during this time. So let's say that it's 10,000 women being followed for 10 years. Over these 10 years, you would expect 4000 plus spine fractures, more than 2500 wrist fractures, and then several hundred hip fractures. This is untreated. If on the other hand, these same women are treated with one of the medications I showed you on the previous chart, we can substantially reduce that number.

Dr. Joy Wu:

So we can bring this from more than 4,000 down to just above 2,000. Similarly, more than 2,500 wrist fractures down to 1,500. And also a significant decrease in the number of hip fractures. So this difference here between the height of the gray and red bars is the number of fractures that we would prevent. There are some extremely rare side effects of these medications that you may have heard of because they've gotten quite a bit of attention in the news. One is osteonecrosis of the jaw. The second is atypical fracture. But I hope this graph shows you just how rare those are. So osteonecrosis of the jaw,

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we can barely see above the baseline. Atypical fractures are really not detectable until somebody's been on the medication for 10 years or more. And for that reason, we now recommend after five years stopping for what I call a drug holiday, that means you pause the medication for a year or two, and then you can safely restart. And that resets the risk of fractures. And so both of these are much less common than say being in a car accident, which is terrible, but rare.

Dr. Joy Wu:

So another way to represent this over those 10,000 patient-years. So a thousand women followed for 10 years. This is the number of fractures that would be prevented by treatment with one of these medications. As compared to the number of expected cases of osteonecrosis of the jaw, so maybe three. Maybe two cases of atypical fractures if women are treated for five years. And you can see this goes up if we go to 10 years. So really this tells us that in appropriate patients, the benefits of five years of treatment far, far outweigh the risk. So again, the number of prevented fractures versus the number that you might expect.

Dr. Joy Wu:

With regard to osteonecrosis of the jaw, I often hear from patients that their dentists or their oral surgeons have some concerns and maybe recommend that they stop. So I think it's important to highlight this statement from the American Dental Association. So this is the professional organization for dentists. In 2011, they issued this statement that said stopping bisphosphonate therapy may not eliminate the risk for osteonecrosis of the jaw. However, stopping these medications may definitely have a negative impact on the outcomes of low bone mass treatment. That's a kind of wordy way to say that if you stop these medications, you will have an increased risk of fracture from osteoporosis. And so therefore, the overall balance of benefits to risks must be considered. So again, the benefits of preventing fractures due to osteoporosis, which is so common, generally outweigh the very, very rare risks of osteonecrosis of the jaw.

Dr. Joy Wu:

All right. So finally, I'm going to turn for a few moments to bone metastases in breast cancer. So about 95% of breast cancer cases in the US are early stage, but the remaining 5% are metastatic. And once it has spread to distant organs, the bone is the most common site for breast cancers to spread. So we know that similar medications that we use for osteoporosis, but in higher doses can prevent the complications of these bone metastases. So here, this was a study of women with breast cancer and bone metastases being treated with Zoledronic acid, IV Reclast. This is the intravenous infusion at slightly higher doses. And they can decrease complications that include things like fractures that need to have surgery or radiation or compression of the spinal cord.

Dr. Joy Wu:

Likewise, Denosumab, which is another medication that prevents bone breakdown is also very effective. This is a study comparing it to IV Zoledronic acid and showing that it may even be a little bit better in reducing these complications. Now, the doses that are used by cancer doctors for metastatic breast cancer are different than the doses that we use for preventing osteoporosis in breast cancer. So I spoke earlier about the intravenous infusion Reclast. That's a five milligram once a year dose. When the cancer doctors use it for metastases, they use it four milligrams every four weeks or every month. So this is almost 10 times higher dose over the year. Similarly, for preventing osteoporosis in breast cancer, we would use Prolia, which is every six months, 60 milligrams. And again, for cancer physicians who are

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treating bone metastases, they use 120 milligrams every month. So this is 12 times the dose. So the risks of side effects are higher at these doses used for bone metastases treatment.

Dr. Joy Wu:

There are a lot of things that we really don't know about how long we should treat. Many of these early studies that were done, that I showed you on treating bone metastases were done almost 20 years ago. Most of those studies were limited to only two to three years of follow up. That was because 20 to 30 years ago, that was the average survival horizon for many patients with metastatic breast cancer. The good news is that survival is increasing dramatically. My colleagues at Stanford showed that since 1990, the median survival has improved by 50% from 20 to 31 months.

Dr. Joy Wu:

And I have a number of patients who are living years with metastatic breast cancer. So that is wonderful news and a real testament to the breast cancer research field and the physicians and patients who've participated in trials to increase those odds. But we're left with a little bit of uncertainty for what to do in terms of how long we should treat, keeping in mind that we of course always want to balance the risks and benefits. And at the doses that are used in these studies, the risk of adverse side effects can be higher.

Dr. Joy Wu:

Finally, I want to point out for anybody who is taking Denosumab, that's either Prolia or Xgeva. I mentioned earlier that it cannot be stopped abruptly, but I just want to make that point again. This is a graph of the average bone density in women who were on the trial for Denosumab, the clinical trial. You can see, they have a really nice improvement over two years of bone density in the spine and in the hip. But the minute that Denosumab was stopped in this trial, that bone density was very rapidly lost so that it was back to baseline within a year after stopping in the spine and in the hip. It even unfortunately fell even a little below the baseline. And this can be associated with spine fractures, multiple spine fractures in some people who stop these medications. So if you are taking Prolia or Xgeva and your doctor mentions that they want to stop, you should know that you can't just stop without doing anything. It really should be followed by either oral Alendronate or the intravenous Reclast, Zoledronic acid.

Dr. Joy Wu:

All right. So I want to leave plenty of time for questions. So these are the take-home messages we have for today. Cancer treatment can affect your bone health. Fractures due to osteoporosis are serious but preventable. Fracture risk depends on many factors that we've reviewed. Lifestyle changes can definitely slow, but they usually don't reverse bone loss, especially when it's serious. When used properly, osteoporosis medications are safe and effective. Just one word, because I saw in the questions, some people were asking about the future. What can we do? So I thought I would just show a few things that we're working on in our research lab. One is trying to convene stem cells to become bone, specifically bone forming cells called osteoblasts. And just showing that we can take skin cells and convert them into bone, which makes minerals stain here in red or down in this slide in black.

Dr. Joy Wu:

And so we've been able to convene stem cells that we harvest from the skin to turn into bone. That's very exciting. And when we implant them in mice, we can actually get some bone formation. These are bone fragments that we can see by x-ray and a CT scan. So that is encouraging because it tells us that

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these bone forming osteoblasts can indeed make bone in a living animal. And we hope that this will have some great applications in the near future for osteoporosis, but also for other regenerative applications like fixing bony defects or trauma or bone destruction. And finally, we've also been looking at bone metastases. I mentioned that we in the clinic avoid bone forming medications for the treatment of osteoporosis because we don't want to raise the risk of metastases. However, as I have told you, osteopenia and osteoporosis are very common with breast cancer.

Dr. Joy Wu:

And the medications that we do currently have are not perfect. They have, again, these rare side effects, but ultimately they can't cure osteoporosis. So we've been very interested in the lab in whether we can use these bone forming medications. And so generally we start with animals and we've been treating with mice. And we've shown that parathyroid hormone, which is marketed as Teriparatide, as a bone forming medication for osteoporosis significantly improves the health of bones and prevents bone metastases. You can see in the mice that receive only saline, there's a lot of destruction from the bones in with breast cancer. However, when we treat them with PTH, I hope you can see many of these bones look much more normal. So fingers crossed that this will turn out to be a therapeutic approach for the future. With that, I want to acknowledge the people in my research lab who do the work, importantly, all the sources of funding I have from the government, from the Mary Kay Foundation and from donors. And with that, I'll stop. And I hope I've left enough time for some questions.

Melissa Rosen:

Wow. Thank you so much. We do have a lot of questions. But interestingly enough, and I think of all the webinars that I've been involved within Sharsheret, maybe more questions than any, but you did an amazing job of answering many of them as you spoke. So I'm going to weed through what we have. Okay. So typical bone density treatment plans, like when to start, what drugs to use, whether or not to take holidays seem based on the assumption that most people start in their sixties. So for those of us who had to start much earlier because of cancer, what recommendations do you have? Do you think that you prefer to put people on medicines right away because of their unique circumstances? Or do you recommend trying lifestyle changes first? And then of course, how long... I know you touched on it a little bit, but how long can these medicines really be used?

Dr. Joy Wu:

Yeah. That's a great question. And this is what I think about a lot from my clinic and my patients. So I think for older women in their sixties or older who are postmenopausal, in a way their management is very similar to anybody else with osteoporosis. But it's the young women, right? So breast cancer does occur in young women as young as thirties and forties. And they're rare, so we don't have a whole lot of information. And that's not a group that's been studied a lot with these osteoporosis trials. So that plus the fact that they are also the ones who are at the highest risk for losing a very dramatic amount of bone, because they are being forced into premature menopause and that can really be difficult on the bones.

Dr. Joy Wu:

So it's a very case by case basis. The recommendations from most societies say that certainly if you're going to be on aromatase inhibitor and ovarian suppression, you should be screened. If you're on tamoxifen, it's a little bit debatable. I'll say that most oncologists at Stanford would send those young women on tamoxifen for a bone density, if for no other reason than to just know what the baseline is

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and where you're starting. And then it's sort of a big picture assessment of where are they starting, what is their bone density, what is the treatment plan. I work very closely with our oncologists. If they're going to be treated with tamoxifen, I might not be so worried. But if they're going to be on an aromatase inhibitor with ovarian suppression, then I'm more worried. And so it's really factoring in everybody, every person's various fracture risks and coming up with a calculation.

Melissa Rosen:

Complicated. Okay. So two questions about bone metastases. So one is if somebody already has weakened bones, bone loss because of age or because of aromatase inhibitors or whatever it is, does that make the bones more likely to... Does that make metastases more likely to go into the bones? I'm assuming it doesn't make metastases more likely, but just maybe where metastases form.

Dr. Joy Wu:

That's actually a very interesting question. And I'm not sure we know the answer to that. I've never seen anything that says that it's more common. But part of what we've been doing our research in is trying to understand why it is that if you increase bone formation, you can lessen the risk of bone metastases. So the converse of that would might be that if you have less bone, maybe you're a little bit more prone. So sometimes those specific questions haven't been asked yet in detail, but I think that's a very interesting research question. I'm going to have to think about that some more.

Melissa Rosen:

Okay. A question just came in and several people asked ahead of time about in addition or in lieu of some of the medicines we're talking about, maybe before somebody needs to go on some of those bone strengthening and building medicines, supplements, obviously calcium and vitamin D. AlgaeCal is something that kept coming up over and over again. Is that something you're familiar with and can speak to?

Dr. Joy Wu:

Right. So the only supplements that really have substantial clinical evidence for benefiting bones are calcium and vitamin D. I'm not specifically familiar with AlgaeCal, but that sounds to me like a version of calcium supplement, which then is fine. But I often get asked about other supplements like strontium. And what's another common one? Vitamin K.

Melissa Rosen:

Boron.

Dr. Joy Wu:

Boron. So strontium for many years was approved in Canada and Europe as a treatment for bone density. It turns out that the bone density improvement is what we call an artifact. It's because strontium looks like calcium. So on a bone density machine, it tricks the machine into thinking that you have more bone density, but it ultimately doesn't prevent fractures, which is what we want. And so it was never approved in the US, but many people would try to get it from Canada and Europe, but they have now withdrawn their approvals. So I do not recommend strontium. It's not beneficial. Vitamin K, there are some studies in animals that are promising, but I generally don't recommend anything until there are rigorous trials that have been done in people.

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Melissa Rosen:

Okay. Some questions about cholesterol lowering drugs interfering with some bone building medicines. So the question is, can you speak to that? And are there any other classes of common medications, antidepressants, cardiac medicine, cholesterol medicine, whatever it is that interfere with any of these?

Dr. Joy Wu:

So that's a great question. Whenever you're taking multiple medications, you want to be thinking about how they might be interacting with each other. What I really love about the medications that I mentioned, the bisphosphonates and Denosumab is they have very, very few interactions. And this is really beneficial because cancer patients are often on a number of different kinds of medications. They might be on chemotherapy. They might be on biologics. Nowadays, they might be on immune checkpoint inhibitors. And so there's a large number of... And then they're on medications for all the side effects that can come as the result of treatment. So the really wonderful thing about the medications we use for osteoporosis is they generally don't interfere with other medications. And I'm not aware of specific data on the cholesterol lowering medications interfering with them.

Melissa Rosen:

Somebody specifically asked in a somewhat related question about the effects of calcium specifically on calcified arteries. Can you speak to that?

Dr. Joy Wu:

Right. So there have been a few reports that calcium supplement might be associated with calcification in your coronary arteries. Those are the arteries in your heart. Those studies are controversial. They were done retrospectively, meaning they were just in studies already done looking backwards in time. And they've largely been reported only by the same groups. So to really believe something from researchers, you want it sort of independently done by multiple groups around the world. That being said, and if you look at the quality of the data, they're not very strong. So I would say for calcium supplements, any link with coronary calcification seems to be at very high doses, like three to 4000 milligrams a day, which I would never recommend, right? I said a 1000 milligrams a day. And maybe there was an association with supplements. So I tell patients if you're really worried about it, then try to get your calcium through diet. But I think most people think that the benefits of calcium in those who are at risk of bone loss far outweighs this sort of controversial risk of calcification.

Melissa Rosen:

Okay. I'm going to ask two more questions and then apologize to anyone whose question wasn't answered. There were a lot of questions about diet and exercise, which I didn't ask tonight specifically because our next two webinars are focusing on nutrition and exercise. But two other questions. One is because we work with so many young women who are dealing with these issues, can you speak to impact on fertility and safety with regard to pregnancy in relationship to these drugs?

Dr. Joy Wu:

Yeah. That's a great question. So I try not to give these drugs to young women for that reason because we often of course are thinking about reproductive potential and childbearing, so we try to avoid it. And usually it's rare, right? It's quite rare that young women would be at risk for bone loss. When you have cancer and especially if it's early or aggressive, some of the usual rules go out the window, right? So then we really have to balance the sum total of the risks and benefits. So again, that's a detailed

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conversation with the individual patient with the oncologist, understanding the individual risks and benefits.

Dr. Joy Wu:

I'll note that the pediatricians are actually quite comfortable with these medications. They use them in children with rare bone diseases like osteogenesis imperfecta. And so my pediatric colleagues often laugh at me for my hesitation to use these. So they say, we use these in young children all the time and they're fine. So I think that some of this is just an abundance of caution, but it is true. Anybody who is pregnant or considering pregnancy, you do want to talk through all of the options carefully with your physician.

Melissa Rosen:

Okay. Last question. Several people asked, assuming a person is gone through cancer treatment, on some sort of aromatase inhibitor, how frequently should somebody get a bone density scan? And then if for some reason, a bone density scan is not the best way to work with someone like maybe someone who has scoliosis and they don't feel like they're getting a good reading, are there any other ways to check bone density?

Dr. Joy Wu:

Great question. So bone density scan, most insurance companies will cover them no more frequently than every two years. And I often tell patients that monitoring your bone density changes is a little like watching grass grow. There's no point doing it too often because you're just not going to see any differences. So for most people it's every two years. There are exceptions. And one of those is again, young women being started on aromatase inhibitor and ovarian suppression. We know that their risk of bone density loss is very high. And they might have a bone density where they start pretty normal, but the oncologist knows that their risk of dropping quickly is higher than usual. And in those cases, insurance companies will cover a repeat bone density scan in one year. And so those are the relatively rare exceptions to that rule.

Melissa Rosen:

And are there other modalities to check bone density if for some reason that type of scan that you showed isn't an option?

Dr. Joy Wu:

Yeah. So we have the most reference information for bone density scans. So sometimes what happens is somebody can't have it in the spine because they've had a fracture, or not in the hip because they've had a hip replacement and there's some hardware, but usually they can either do the other hip or sometimes they can check your wrist. So you can check other sites and get some information. We can assess bone density from special kinds of CT scans, but they are rare. We don't have a huge amount of information and they come with much higher doses of radiation. So again, it's a conversation with your doctor if you fall into that category about what your options are.

Melissa Rosen:

So I am going to stop with the Q and A for now. Thank you for answering so many questions. I want to be respectful of everybody's time. And I want to thank you for educating us this evening. I don't know if you were able to see, and even I was only catching a few of them, but so many positive comments in the



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chat about how clear, how informative. So thank you. Please take, I'm going to encourage everybody on to take a moment to fill out the brief evaluation survey that's being linked in the chat box right now. Evaluations really do inform future programming. So thank you in advance. And of course, we'd love for you to stay connected with us on social media, Facebook, Instagram, Twitter, where we post about events like this, program updates, and fun ways to get involved. Once again, I want to thank Amgen, our sponsor for today's webinar, as well as the upcoming two webinars on bone health and nutrition, and bone health and fitness.

Melissa Rosen:

So many of the questions that were asked today we didn't get time to answer will be answered in depth in those two. In the chat right now is the link to register for the next one, which is bone health through nutrition with nutritionist, Tamar Rothenberg on March 15th. Please remember that Sharsheret is here for you and your loved ones during this difficult time in your lives. Sharsheret provides emotional support, mental health counseling, and other programs designed to help you navigate through the cancer experience. All programs are free, completely private, and one on one. Our number and our email address is in the chat right now. And our social workers and genetic counselor are available to each of you. Thank you again for joining us. Thank you again, Dr. Wu. And thank you to everybody and good night.

Dr. Joy Wu:

Thank you for having me.