Advancing Breast Cancer and Ovarian Cancer Research in Israel: Latest Discoveries & Innovations

National Webinar Transcript

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Presented by:

SHARSHERET®
The Jewish Breast & Ovarian Cancer Community

About Sharsheret

Sharsheret, Hebrew for “chain”, is an international non-profit organization, that improves the lives of Jewish women and families living with, or at increased genetic risk for, breast or ovarian cancer through personalized support and saves lives through educational outreach.

With regional offices in the Midwest, Northeast, Southeast, West, and Israel, Sharsheret serves 275,000 women, families, health care professionals, community leaders, and students. Sharsheret creates a safe community for women facing breast cancer and ovarian cancer and their families at every stage of life and at every stage of cancer - from before diagnosis, during treatment and into the survivorship years. While our expertise is focused on young women and Jewish families, approximately 25% of those we serve are not Jewish. All Sharsheret programs serve all women and men.

As a premier organization for psychosocial support, Sharsheret works closely with the Centers for Disease Control and Prevention (CDC) and participates in psychosocial research studies and evaluations with major cancer centers, including Georgetown University Lombardi Comprehensive Cancer Center. Sharsheret is accredited by the Better Business Bureau and has earned a 4-star rating from Charity Navigator for four consecutive years.

Sharsheret offers the following national programs:

The Link Program

Peer Support Network, connecting women newly diagnosed or at high risk of developing breast cancer one-on-one with others who share similar diagnoses and experiences

- Embrace™, supporting women living with advanced breast cancer
- Genetics for Life®, addressing hereditary breast and ovarian cancer
- Thriving Again®, providing individualized support, education, and survivorship plans for young breast cancer survivors
- Busy Box®, for young parents facing breast cancer
- Best Face Forward®, addressing the cosmetic side effects of treatment
- Family Focus®, providing resources and support for caregivers and family members
- Ovarian Cancer Program, tailored resources and support for young Jewish women and families facing ovarian cancer
- Sharsheret Supports™, developing local support groups and programs

Education and Outreach Programs

- Health Care Symposia, on issues unique to younger women facing breast cancer
- Sharsheret on Campus, outreach and education to students on campus
- Sharsheret Educational Resource Booklet Series, culturally-relevant publications for Jewish women and their families and healthcare Professionals

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Pnina Mor: Thank you for joining us tonight. I am honored to be hosting the first Sharsheret in Israel webinar. I am Pnina Mor, director of Israel Support Services for Sharsheret in Israel. For those who don't know me, I am a nurse midwife and through midwifery I realized the necessity in promoting women's health through her lifespan with the emphasis on breast and ovarian health.

As a result of my studies and doctorate, I opened in 2007, the first multidisciplinary one-stop shop clinic for BRCA mutation carriers in Israel, and the world, the NOGA Clinic. Over time, together with Liora Tannenbaum, we recognized the need for Sharsheret support for the English-speaking community in Israel, and together we started the Israel branch of Sharsheret in Israel.

I have a few housekeeping items that I want to go through before we actually start. So today's webinar is being recorded and will be posted on Sharsheret's website along with a transcript. Participants' faces and names will not be in the recording. You may have noticed that you were muted upon entering the Zoom, please remain muted during the call. We'll hold a Q&A at the end of the presentation. If you have any questions during the presentation, please type them into the chat box and we'll get to as many as we can.

I want to remind you that Sharsheret is a national and now international not-for-profit cancer support and education organization and does not provide any medical advice or perform any medical procedures. Our full medical disclaimer is in the chat.

As I said, this is our first webinar in our new series highlighting cancer experts from Israel. Sharsheret opened its office in Israel one year ago to expand Sharsheret's mental health support and educational programs. We are now offering in Israel to English speakers confidential and local one-on-one emotional support and mental health counseling, patient navigation to work through the complex Israeli medical system, peer support to connect with other Israeli women facing similar situations and diagnoses, and virtual support groups, which we are now currently recruiting for.

If you or someone you love is facing breast cancer, ovarian cancer, or increased genetic risk for cancer and is living in Israel, please don't hesitate to reach out. Below is our Sharsheret Israel website and my contact information.

Before we welcome our experts to the screen, I am happy to welcome Michal Gorlin Becker to share her story. Michal.

Michal Gorlin B...: Hi, my name is Michal Gorlin Becker. I'm originally from Silver Spring, Maryland and have been living in Jerusalem for almost 28 years. I'm married and have four children.

To make a long story short, I have long known that I was high risk for ovarian and breast cancers. My grandmother beat ovarian cancer in the 1960s and my great aunt died of it. My mother beat ovarian cancer in 2009 and then beat breast cancer in 2014. So we were in no doubt that there was a genetic component, even though I was consistently testing negative for any BRCA mutation.

Thanks to the help of genetic counselors and doctors in Shaare Zedek, regardless of my BRCA standing, I was screened early and often, and in 2016 I had a prophylactic oophorectomy. And in 2020, on my 46th birthday, just as corona was rearing its ugly head and medical appointments were being canceled worldwide, but thankfully not in Israel. Dr. Strano's brilliant diagnostic skills caught my breast cancer from an ultrasound, not a mammogram, at a super early stage.

Immediately after being diagnosed, I learned more about my genetic makeup, thanks to my close friend, Dr. Michaelson-Cohen, who insisted that I get genetic tested yet again. This time we discovered that I carried a then newly identified BRCA1 mutation. This was significant, not just for my understanding of my own health and the health of my family, but for how it influenced my treatment decisions, opting for a double mastectomy instead of a lumpectomy. And I had always told myself that if I was BRCA positive, I wouldn't hesitate and I'd do the double mastectomy. So after eight rounds of chemo and then the surgery, I thank God came out on the other side with a clean bill of health.

One of the few perks, very few perks of being BRCA positive, is that I get access to the NOGA Clinic, which Pnina Mor started. The clinic offers individuals like me, those with BRCA mutations, a one-stop-shop for everything from mammograms and ultrasounds and to emotional support. And now I'm lucky enough to work with Pnina and Liora who have helped bring Sharsheret to Israel. Sharsheret was there for my mother when she was sick, and then for me when I was, so I couldn't be more thrilled to be involved with the organization. Cancer is a long hard road, but with the right people, the right resources and the right mindset, the road is conquerable. Thank you.

Pnina Mor: Wow, thank you so much, Michal. Every time I hear her speak, it brings tears to my eyes. Hearing personal stories really, really makes it easier for everyone to understand this information.

So tonight we are honored to be joined by Dr. Rachel Michelson-Cohen, who's the director today of the BRCA NOGA Clinic in Shaare Zedek Medical Center in Jerusalem. Dr. Tal Sella, breast oncologist from the Sheba Medical Center in Tel Aviv. And Dr. Naama Srebnik-Moshe, director of the Reproductive Endocrinology Services at the Shaare Zedek Medical Center in Jerusalem. Both Dr. Sella and Dr. Srebnik are also members of the Sharsheret in Israel's Medical Advisory Committee.

I'm going to call on Dr. Michaelson, but first a few words, a little bit about her. All our guests' bios can be found on our website. So Dr. Rachel Michaelson-Cohen is a senior physician at Shaare Zedek Medical Center in the Department of Obstetrics and Gynecology and the Institute of Medical Genetics. Dr. Michaelson is the clinical director of the prenatal genetic unit and has recently been appointed as medical director of the BRCA NOGA Carrier Clinic. It's all yours. Thank you.

Dr. Rachel Mich...: Good evening. I'm honored to be the first speaker in the first webinar. Thank you very much for inviting me to share this information with you. The first talk is going to be about implementation of the first nationwide BRCA screening program. Israel was the first and is still the only place in the world that is performing BRCA screening for the population.

Pnina Mor: Do you want to share your screen?

Dr. Rachel Mich...: Excuse me, I thought I was. Sorry.

Pnina Mor: Great.

Dr. Rachel Mich...: Okay, so I'm going to be speaking about implementation of the first nationwide BRCA screening program.

So why do we screen for BRCA in Israel? It turns out that breast and ovarian cancer were the leading cause of death in Israeli women in 2020, and we need to do whatever we can to fight cancer. Identifying BRCA carriers reduces cancer mortality through high-risk surveillance. Until a couple of years ago, the only women who had BRCA testing were those who had a genetic mutation in their family or women who themselves had breast or ovarian cancer.

So we looked at screening the general population for BRCA mutation as opposed to testing only people that are high risk. And it turns out that not only would screening the entire population according to the models that we checked before we actually started the screening program, it turns out that not only does it prevent cancer and death, but it also saves the country money, which is

what's called... Cost effectiveness. And so after we published our findings, we finally managed to get the BRCA screening program funded by the Israeli Health Ministry after submitting it a few times to the health basket. And in 2020 it was finally approved after we published that article in cancers.

However, in 2020 COVID hit and no one was doing any screening of any sort. But late in 2021, the HMOs in Israel started the screening and we set off. And Israel, as I mentioned, is the first country that has a nationwide BRCA genetic screening program, which we're now doing across the country in all HMOs.

So who can be screened for BRCA? Well, basically everyone, if you're an Ashkenazi Jewish woman and you don't have to be fully Ashkenazi Jewish, it's enough that you have one grandparent. If you're female and over 18 and have no known family mutation, you could be screened for BRCA.

Screening actually depends on multiple steps. I assume that everyone here has heard of the BRCA mutations, but not everyone in the general population has. So we really need everyone to be aware of it. We need the public to be aware and we need all the HMOs sending out the text messages to women. So that's what we've been doing for the last few years. And we've also been raising awareness among physicians who are referring their patients to be tested. We have many gynecologists who are referring people, breast surgeons and any other physician basically. Once women make their appointment to be screened, they'll get written information or they'll hear about it from the nurse practitioner. They will not go through genetic counseling because up until now, again, women were only tested after having genetic counseling because of familial history. After filling a questionnaire, the blood is drawn and then women will be getting their results a couple of months later.

Now, most women who screen for BRCA will be negative. As we know in the Ashkenazi Jewish population, it's about a two and a half percent chance. So if we're screening the general population, most women will turn out negative and you'll get your result on your app or online. However, if you're positive, and it's always a surprise, you're going to get an unscheduled phone call. After receiving that phone call, you're going to hope to get an appointment for genetic counseling within a month and within a month of the counseling, hopefully you will find a spot in one of the high-risk BRCA clinics.

So we have about 900,000 Ashkenazi Jewish women in Israel, and so far about 160,000 of them have been tested in the different kupat holim, which means that almost 20% were tested, which is a lot within three and a half years. And actually the rate has been, according to that, about 55,000 women testing annually, out of whom about 650 new carriers just from screening have been diagnosed. Don't forget, many women are still testing through the regular traditional genetic counseling.

So when we looked at the numbers in NOGA from mid 2021, which is when the population screening actually began in Israel until the end of 2024, it turns out

that most newly diagnosed BRCA carriers were diagnosed through the screening and not through traditional genetic counseling. So what we wanted to do in our study was to compare women that were diagnosed through the population screening versus women who were tested through the traditional genetic counseling because of their family history, or family mutation.

So we wanted to compare these women by... And don't worry, this is not very long, we're just going to have one slide on each topic, characteristics of the different women, risk-reducing actions, psychosocial outcomes, which we collected according to their records and questionnaires that they filled out. And then we actually interviewed a bunch of these women to see what their experience was.

So when we compare the characteristics on the left, you could see the group of women that came through the regular genetic clinics because of a mutation in their family or some high-risk family history, and on the right women who came through the population screening, who again did not have a very high-risk family story. And you could see that the women were the same basically, meaning the P-value was not significantly different, for most of the things we looked at, which were age. Most women tested were in their late 30s, most women were college-educated, more than 80% were married and more than 70% had children. The only real difference between the groups was their risk by family history, which is quite obvious.

So we saw that women that came through traditional genetic counseling were mostly in the moderate high-risk group in terms of their family history, whereas the women coming through population screening mostly did not have such high-risk family history. The women who came through the population screening were also more likely to be Ashkenazi Jewish because don't forget, there are mutations in other populations and they had more of the BRCA2 gene versus the BRCA1 gene for different reasons.

In terms of risk-reducing surgery, I'm showing here the results of the oophorectomy, which we recommend to all BRCA1 women over 40 and all BRCA2 women over 45. So you could see that there was a very high uptake in both groups, and we didn't find a difference between the group, which means that even women who did not have a history, it was enough that they got a positive mutation result and listened to our counseling and went ahead and removed their ovaries. There also wasn't a difference in the time that it took them from being diagnosed as a carrier until removal of ovaries.

So what we were worried about actually was what's going to happen to these women in terms of their anxiety, in terms of their satisfaction with being tested? Would they regret being tested? Would they have a lot of stress? So this is a whole bunch of psychosocial outcomes, which we compared between groups. And you could see again, the numbers and the scores here are very similar between the groups, and women in general in both groups did not have a high anxiety result, and they were mostly satisfied. If you look at the general

satisfaction score from one to five, women had about a four, and that was the same in both groups. There were slight differences, especially with the pre-test information and with the delivery of results. But overall, the general satisfaction was the same. And when we did a multivariate analysis which controls for different factors, there were no real differences between the groups, which means that not only did women receive their information and go through surgery, they also generally were okay.

We also interviewed some of these women to learn from their experiences, and we saw that there were common themes in both groups. But in both groups, women tested because they wanted to know what their cancer risk was, they wanted to be responsible towards themselves and their families, and no one was happy with the result. Meaning when women got the phone call about being a carrier, most women were sad and were afraid of cancer. Nevertheless, over time in both groups, women were generally satisfied and happy that they tested because they realized that that would improve their prognosis.

So what was unique about these women in the population screening? Again, this is the first time we're doing it on a national basis. So a lot of the women said that they were tested just because it was on a checklist. They had heard about it through an advertisement or their doctor had told them to go be tested, but they didn't think about it very much, which is not something that happened when women go through genetic counseling. And it turns out that the less women thought about it before, the more shocked they were when they got the result that they're carriers. Remember, most women get a negative result, and those one to 2% that got their positive results were really shocked with the results. They got over it eventually, but it was difficult for them.

These women really prefer to be cared for in dedicated high-risk clinics and less so in community centers, and they also stress the need for awareness. A lot of the women mentioned the fact that there's not enough awareness in the general public and there's not enough awareness among healthcare caregivers. A lot of them mentioned that they would have preferred getting the results from the physician that treats them rather than a phone call. And a lot of them mentioned that they're having trouble making appointments for a high risk clinic.

So I'll share our conclusions with you. As I mentioned, this is the first nationwide population screening, and it does help avoid bureaucracy. There are many more women being tested and we have very high numbers of women going through preventive surgery. Most of them are satisfied that they were tested and with their health decisions, and the data does support continuing this population screening. We do need to look at certain things of improving the way we carry out this screening, and we need to follow up long-term to see the outcomes.

Cancer has already been detected because of our population screening, and I could tell you that in the NOGA clinic from about 200 women who were tested because of population screening and not because there was cancer in their

family. We already diagnosed eight cases in this short period, five cases of breast cancer and three cases of ovarian cancer. Almost all these were early stage with good prognosis. Risk-reducing surgery has likely prevented many other cancers that we'll never even know about because women had preventive surgery. Population screening should be done for women between 25 and 30 years so we can allow early diagnosis and prevent cancer on time. And of course, we'll need long-term evaluation in order to calculate how many life years we gained and quality of life years, which is even more important.

So if you're an Ashkenazi Jewish woman and you have not been tested for BRCA, please do so by making an appointment in your kupat holim. It's free and you don't need a doctor's referral. You just have to ask for a “hafnaya” - referral for BRCA testing. If you're in Meuhedet, you will need to ask your family physician for a referral, and most of you hopefully will be negative, but if you are positive and you are looking for a high-risk clinic, we can help you, and here is the email of the NOGA Clinic.

I'd also like to invite you all if you're interested. This will be in Hebrew, but we'd be happy to see you in our event that we're having next week in Shaare Zedek at 7:00 in the evening, and Pnina can give you the details. We'll be discussing preventing breast cancer, we're going to have a breast surgeon and a plastic surgeon discussing these, and we'll be happy to see you there.

With that, I'd like to say thank you to all of my collaborators in Shaare Zedek and elsewhere, including Dr. Naama Srebnik, who will be speaking shortly. Thank you very much to Pnina who founded the NOGA Clinic and has done a lot of this work. I want to thank our volunteers, including my mother, Serena, who is listed on this slide. This research has been funded by the Breast Cancer Research Foundation, the Israel Cancer Association, and the Israel Cancer Research Fund. Thank you for listening, and I'll be happy to take questions.

Pnina Mor: Thank you. Thank you very, very much. We're going to have the questions afterwards. I just want to remind everyone to please remain mute, and if you are not muted, then mute yourselves and then we're going to continue to our next speaker.

Dr. Tal Sella is a senior breast oncologist at the Sheba Medical Center. He completed a clinical and research fellowship in the treatment of breast cancer in young women at the Dana-Farber Cancer Center in Boston in the States. His research concentrated on the unique characteristics of breast cancer in young women, including biological and therapeutic aspects, as well as their short and long-term effects on the quality of life and general health of patients. Dr. Sella, it's all yours.

Dr. Tal Sella: Okay, thank you, Pnina. Thank you everyone. Let me share my screen.

Okay, so Pnina asked me to discuss what's new in breast cancer, and there's a lot happening, but I thought we could focus on ER/PR-positive or hormone receptor-positive breast cancer, which is the most common kind of breast cancer. About 70% of breast cancers are hormone receptor-positive and HER2-negative. So I thought that would be a good place to start. There are my disclosures.

As a general overview, I'd like to remind or teach someone, anybody who doesn't know that when we treat breast cancer or early breast cancer, we have local therapies, surgery and radiation. As medical oncologists, we deal a lot with the systemic therapies that are meant to prevent recurrence of breast cancer later in life. Specifically for hormone receptor-positive breast cancer, we have endocrine therapies like tamoxifen, aromatase inhibitors. And recent years we've been giving more and more ovarian suppression injections. For some women, we offer chemotherapy. And over the last decade, a lot of the chemotherapy use is directed by genomic risk assays that try to predict the risk of the cancer and therefore the potential benefit of chemotherapy.

And then a few of the things that I'd like to talk about today are some of the novel and emerging therapies. So in my talk, I'll actually focus on three areas that I think are particularly interesting and evolving. One will be chemotherapy, a little bit about the controversies and things that are happening in that field, and then about the new therapies that we've seen approved in the last couple of years. These are adjuvant therapies, and treatments that we add to our hormonal therapies. There's CDK4/6 inhibitors and oral SERDs, which are a new kind of hormonal therapy. So we'll get into that.

So we'll start with the genomic tests and how they predict chemotherapy benefit. And as they said, for probably a decade and more we've been using these tests. A very common one, particularly in Israel, is the Oncotype test. It's a test that looks at 21 genes or the expression of these genes in the cancer and summarizes this... The gene's expression into a score. And that score is associated with the risk of cancer recurrence and with the benefit of chemotherapy.

And so several years ago, this study was published, a very important study, where women with early hormone-positive breast cancer, the cancer did not involve their nodes. All of them had the Oncotype test before they started their therapy. If it was very low, they received hormonal therapy, if it was very high, over 25, they received chemotherapy, and if it was in the middle, between 11 and 25, that's where the trial happened, and they were randomized to either receive only hormonal therapy or hormonal therapy and chemotherapy.

And this is a really important study. The study was positive. It showed that women with an Oncotype in that range, 11 to 25, don't benefit from adding chemotherapy to hormonal therapy. So potentially we're able to omit chemotherapy from the treatment of many women. But one of the interesting findings here was when they looked by age, they found that the overall

conclusion was correct for postmenopausal women over 50, no benefit from chemotherapy. But in younger women, those under 50, there seemed to be a benefit from chemotherapy. And you see that in the left, the bottom left corner here where there are two lines, a dotted line, which shows the risk of recurrence of hormonal... For women treated with hormonal therapy and chemotherapy, and the solid line shows the risk of recurrence for women treated with hormonal therapy alone. And you see how they diverge on the right for postmenopausal women, the lines don't diverge.

So this benefit was age-specific, and that doesn't really make sense. Why would a cancer behave differently according to the women's age? And one of the interesting things that they showed is that if they look at the age groups between 50, this is what we call a forest plot. So when these boxes are on the right, it shows increased benefit from chemotherapy. And as you can see, the women who have most benefit from chemotherapy are actually not the youngest women, not those under 40, but those who are between 41 and 45, or the premenopausal women, age 46 and 50.

And this was a really intriguing observation. And the hypothesis driving this is that this has to do with the hormonal effects of chemotherapy that in these older premenopausal women, chemotherapy might be pushing them into menopause. So chemotherapy might be a form of ovarian suppression. And then comes the question that if it's all about ovarian function suppression, maybe we can achieve that with shots and not with chemotherapy. So there's a very big question on whether these younger women actually, how much of this benefit is driven by chemotherapy and how much isn't.

And there was another trial also with the Oncotype test in women with no positive breast cancer. And this trial also showed the same thing. No benefit for chemotherapy in postmenopausal women, but a benefit restricted and limited only to premenopausal women. Again, something is happening with the ovarian function. Something hormonal still can't exclude that some of it is direct chemotherapy benefit in different tumors, but it is an intriguing observation. As this year, the investigators from this last trial, RxPONDER, looked at AMH.

AMH is a hormone that correlates with ovarian reserve. When it's low, there's a low reserve, when it's high, there's a higher reserve. And so it's a much more sensitive marker for menopause. And they found something interesting. First of all, they found that when even women who considered themselves to be premenopausal were having periods, some of them already had very low AMH, and could be considered in the postmenopausal range. And when they looked and divided women into two groups, not by age this time, and not by having periods or not having periods, but by the AMH status, by their ovarian reserve, they found the same findings that we showed earlier, that women with a low AMH, low ovarian reserve, did not benefit from chemotherapy probably because they would go into experience menopause with chemotherapy. Those with a higher AMH seem to benefit from chemotherapy.

So what's happening now, there's a very big trial in the US and all around the world, primarily in the US looking to really understand how much of this is the chemotherapy and how much of this is the ovarian function suppression. So for women with an Oncotype in these intermediate ranges where there might be a benefit from chemotherapy, truly really trying to pin out how much of this is driven by the chemotherapy, how much of this is because of the ovarian function effects of the chemotherapy. And maybe in the future we'll be able to omit chemotherapy for even more premenopausal women. And I think this is a really important trial that people should look up if it's available to them.

The second thing I want to talk about is the CDK4/6 inhibitors. These are drugs that have been available for metastatic breast cancer for several years. And recently we had two studies published that showed that if you add them to adjuvant hormonal therapy, so hormonal therapy like tamoxifen or an aromatase inhibitor, which is given for five to 10 years, if you add these CDK4/6 inhibitors for another two to three years, we can reduce the risk of recurrence even more.

So the first trial is called monarchE, this is CDK4/6 inhibitor called abemaciclib, that's administered for two years, and they showed that with five-year follow-up following the addition of abemaciclib for two years, the risk of recurrence was decreased by seven and a half percent. It's important to note that if you look at the women who were included in this trial, so this is a really high-risk subpopulation of women, all had cancer in their nodes and an additional risk factor for recurrence. But for these women who have a high-risk of recurrence, we now have even more effective treatment. So this is something that all women really should know about and ask their doctors about.

The second trial also with a CDK4/6 inhibitor is called NATALEE. This trial also looked at a high-risk population of women a little bit more, I'd say intermediate risk. Similar to the prior trial, they added ribociclib, a different CDK4/6 inhibitor to hormonal therapy. This one was given for three years, and they also have shorter follow-up. It's only four years, but at four years, they already see a 5% drop in recurrence. So really important, and this is treatment that we have available in Israel and I've been prescribing.

So we have two approved drugs at the moment, both reduce the risk of recurrence. Abemaciclib is the one that's in the Israeli health basket. It's indicated for a little bit more high-risk population. Ribociclib also includes a lower-risk population, I'd say an intermediate or moderate-risk population, including some women who have stage two node negative breast cancer. If we have time later, we can discuss and contrast these treatments. But of course, any new treatment has benefits, but it also has side effects. And adherence is a problem. It's a problem with hormonal therapy, and it might even be more of a problem when you add these drugs.

Lastly, just to look into the future, so for the last probably two or three decades, our hormonal therapy has been mostly tamoxifen and aromatase inhibitors. And

currently today there are multiple new kinds of hormonal therapies in development. Most advanced is this category called SERDs or selective estrogen receptor degraders. Some of these drugs are already approved for metastatic breast cancer, and there are multiple trials in the US and around the world, including in Israel, we have three of these open at Sheba at the moment, trials that are looking to see if these new forms of hormonal therapy might be better for the prevention of recurrence of early breast cancer. So we're trying to see if they might be better than tamoxifen, better than aromatase inhibitors.

There are trials that are giving them upfront as the first hormonal therapy. There are trials that are giving these new drugs after a few years of the regular current standard hormonal therapies. And these are also really important, very big international trials that I think will have a very big impact on how we treat breast cancer in the future. And I think it's really important for women to know about them and hopefully volunteer to participate in them if they're available. So thank you all for listening, and I'd be happy to take questions later on. Thank you.

Pnina Mor: Wow, thank you. Thank you very much. We're going to go on to Dr. Naama Srebnik-Moshe, who's a specialist in obstetrics, gynecology and fertility. She is a senior physician in the Department of Obstetrics and Gynecology, and in the in vitro fertilization, the IVF unit, as well as director of the reproductive endocrinology services at Shaare Zedek Medical Center. In addition to her hospital position, Dr. Srebnik is a senior lecturer at the Faculty of Medicine at the Hebrew University. She's a coordinator of the BRCA medicine course at the Tel Aviv University. She's member of Israeli Society of Pediatric Adolescent Gynecology and the Israel Menopause Society. There you go. Where are you? Dr. Srebnik, it's all yours.

Dr. Naama Srebn...: Okay, so I'm here. So I have only four issues that I want to discuss with you in these very short 10 minutes, and we're going to try to rush through these issues. One second. Let's see that it's working.

Okay, so what we want to talk about, we want to talk about contraceptives. We're going to talk about PGT, preimplantation genetic testing, about the timing of BSO, and more specifically about what we're going to do after the operation about the hormonal treatment.

So let's start with the contraceptives. There's always a question, is it safe? Is it okay? Does it increase my risk for breast cancer? So we know, and there's a lot of data in the literature. I just brought one study, it's a meta-analysis and many, many studies showing that treatment with contraceptives, oral contraceptives, hormonal, lower the risk of ovarian cancer by 50%. It's very, very impressive. The only question is, does it really matter to the BRCA carrier who is about to take the ovaries at an earlier age, around 40 or 45?

So I think the main question about using combined hormonal contraceptives is does it increase the risk for breast cancer and not the ovarian cancer? Also, for

that, there are a lot of studies, many studies show conflicting results. And this is why I want to show you only one of the latest studies on BRCA carrier patients asking specifically, what does it do to breast cancer risk?

And we can see that studies basically spread into two groups. We have one group that shows that there is a slightly increased risk of breast cancer for women using combined hormonal contraceptives. And other studies show that there is not an increased risk. So it's really conflicting, and it's really hard to say, and this is why today what we recommend the patient is not, you don't have to take contraceptives just to lower an ovarian cancer risk or whatever, but you can use it if you need it. If you want to prevent pregnancy, and this is the option that is good for you, you can use combined hormonal contraceptives, probably it will not increase your risk. And even if it does, it's very slight increase risk of breast cancer.

Okay, so this is a summary what we're talking about the ovarian cancer, we're talking about decreased risk, but it's not clear the meaning when BSO, bilateral salpingo-oophorectomy, is planned and about the risk. Some studies show increased risk, other found no increased risk. So it's whatever the patient is feeling that is good for her, and there's no recommendation to take medication on a regular basis.

So let's talk a little bit about the inheritance. Now we know that BRCA is inherited, an autosomal dominant inheritance. That means that 50% of offsprings might be affected and it can come through maternal inheritance or paternal inheritance. And this is why it's so complicated to find the carriers, because many patients basically have a family history coming from the father, and this is why they're sometimes not diagnosed early. So the question is, do we have an option to prevent the inheritance to the next generation?

And there is an option, although we will discuss its complexity, and that is called preimplantation genetic testing. When you undergo IVF treatment, in vitro fertilization, and every embryo is biopsied and all the embryos that are healthy are transferred back to the uterus. But there are many, many ethical issues around this procedure. First, we know that not all BRCA carriers will be affected, and it makes a question whether not implanting back an embryo that is just like me, I am a carrier, I'm a healthy, so how come I will decide not to have me born? It's an older age disease. So again, it's a question, is it enough for us to choose who will continue, who will not? It's not exactly a live or die because it's an embryo, but it's something very complex.

There are preventive strategies. We know that we have preventive strategies, there is potential genetic cure in the future. We know that the genetic system is very, very progressed, and they might find a way to cure BRCA gene. We don't know. What about the carrier embryos? What do we do with them? Is it do we save them, do we implant them back, do we discard them? It's complicated. And again, the patient has to undergo IVF, which is quite a bearing.

So what do people decide? So we have lots of studies about the decision-making related to PGT in BRCA carriers around the world. And it seems that women who have a family history of breast cancer or ovarian cancer are more tending towards doing PGT. And men also, which is probably because they don't have to undergo the treatment, and this was the main influence towards the decision. And also a study made by Dr. Pnina Mor in Israel in Shaare Zedek, the main issue that made patient decide if they want to undergo PGT is if they had an infertility that forced them to undergo IVF anyway, so it was easier that we have the embryo in the lab, we just test it. So it was easier to make the decision to undergo the PGT.

Another issue is the ovarian reserve that was mentioned in the previous lecture. There are several studies that try to say that BRCA carriers have lower ovarian reserve, and this is why it's going to be more complicated to treat them because we're going to have less oocytes and less embryos. So several studies did show low response to stimulation during IVF treatment, lower AMH levels, but other studies, specifically studies in Dr. Michaelson-Cohen, and another study that I was part of, the writers of it, from Sheba and Shaare Zedek showed that the number of eggs was the same and the ovarian reserve markers were the same between BRCA carrier and the general population. And there is right now a very large study conducted in Shaare Zedek that probably will show the similar results that ovarian reserve markers are the same in BRCA carriers. So this should not be an issue.

Another question, which I think is quite a heavy one, is, does this treatment increase my risk to have breast cancer? We know that there's a lot of fuss about it. Does the hormonal treatment increase the risk? Although most of the studies do not show increased risk for breast cancer in IVF, we have a very large study conducted in Israel right now. The results are still not published, and once we'll have them, we will let you know. But these are quite large studies, and not in Israel specifically, but we can see that 25,000 women with an average follow-up of 21 years, there was no increased risk of breast cancer of patients undergoing IVF cycles. Some of them even underwent 11 cycles. So I think it's quite safe.

And we can also say that it's quite safe for BRCA carriers because there are several studies also conducted on BRCA carrier patients, and one of them is also an Israeli study. And in the Israeli Jewish population of carriers, no increased risk for breast cancer after fertility treatment or IVF was found. So again, it's quite safe and this is a good option, and if someone needs it, they can use it.

We still have the question of what to do with affected embryos, specifically male embryos, because usually female embryos are not transplanted. But do we transplant a BRCA2 male embryo which has a risk for disease, BRCA1 carrier that can pass the disease to the next generation. But if the patient has recurrent failures and undergoing many IVF cycles, maybe then we will transfer BRCA carrier embryos if they also have infertility. These are major questions that have to be discussed with the patients. And sometimes we see the patient starts the treatment of PGT, but then they turn around and they just say, "Okay, we're

going to pass down." And it's quite complicated to discuss these issues with them.

But whatever the patient chooses, PGT or not PGT, unless the family planning has started, specifically today when we have a larger population of single women that don't want to be pregnant right now, we really recommend fertility preservation at an early age. The reason is that the older the age, the lower the oocyte quality. And if the patient will want to... The woman, it's not a patient, will want to undergo PGT or just try to conceive later after undergoing bilateral salpingo-oophorectomy, then we want the oocytes to be young because then we're going to have higher chances of having a pregnancy. So we recommend undergoing fertility preservation around the age of 30 up to 34. The earlier the better, because oocytes at the age of 40 are quite less good compared to the age of 30.

So we are done with family planning, we have all the kids that we want, and now we know that there's no way to detect early an ovarian cancer. So we have no other options but to undergo risk-reducing bilateral salpingo-oophorectomy. So we're going to take our ovaries out. Then the NCCN guidelines talk about age 35 to 40 if you're a BRCA1 carrier, and 40 to 45 if you're a BRCA2.

So we completed our family planning. That's not the issue. But does it have a cost, the fact that we took out our ovaries at the age of 35? And what are the consequences of BSO? So we know that estrogen is a hormone that is highly important in the female body. I don't think there's even one major system or tissue that doesn't have receptors to estrogen. It's the cardiovascular system, liver, pancreas, adipose tissue, bone marrow, musculoskeletal, cardiovascular. Everything has something to do with estrogen. So if we took out the estrogen from the system, we took out the ovaries, all of these systems might be affected.

And if we only talk about menopausal symptoms, we can talk about hot flashes and night sweats and disturbed sleep and decreased concentration and mood swings and decreased memory and weight gain and all other issues. And this is just the symptoms, but there's also a health issue related to the oophorectomy. And there are several studies that examined mortality risk undergoing oophorectomy at an early age. And this is only one study, and there are many studies that showed exactly the same results. This is a very large study, this is why I brought it. They examined the non-cancer mortality according to the age in which the oophorectomy was done. And as you can see, we have 53,000 patients. This is quite a large number.

What you can see is the earlier the age the oophorectomy was done, the higher the risk of death, okay? So this is under 35, this is under 40, this is under 45. Okay, so we're talking about a major issue. Oophorectomy increases a death risk. Of course, it's not so significant. The ovarian cancer is much more dangerous, but still, there's something here that we need to discuss. And if we see another study, and then we can see that all cause mortality if patients were

under 45 at the operation was 1.5, okay? So we have a 50% increased risk of death, mainly because of coronary heart disease and also dementia and Parkinson's. So we cannot just say, okay, go through oophorectomy and then just survive. No, we have to offer a treatment. These are all the consequences of early ovarian failure. And in our case, oophorectomy, we're talking about cognitive impairment, cardiovascular, impact on bone health, autoimmune and thyroid disease, genitourinary syndrome and mortality.

So what do we recommend? We know that the North American Menopause Society position statements say, okay, we have to replace if someone's out, we have to bring them in somehow. Okay? So we have to replace through given in the hormones. And the average age of treatment must be until the average age of menopause, which is around 51 or 52. And until then, patients need to get hormones. Some of the women will need higher doses. And the most important thing is to protect the heart and the bone.

But is it safe? Is it safe? Because as the patient says, "I'm a BRCA carrier and I have an increased risk for breast cancer, and someone told me that hormones are dangerous for the breast." So we have a few studies, none of them are very long-term, okay? There are studies on four years and seven and a half years. We don't have studies on 20 and 30 years in carriers. But most of the studies show similar risk for breast cancer. If you took hormones or you didn't take them, we're talking about women that underwent oophorectomy at an early age because we're not giving extra hormones, we're just replacing normal hormones that the woman was supposed to have, okay? So we have several studies showing that there's no increased risk for breast cancer in these patients taking hormones until the average age of menopause. This is another study that-

Pnina Mor: Naama?

Dr. Naama Srebn...: Yeah?

Pnina Mor: We have to soon finish up.

Dr. Naama Srebn...: So yeah. Yeah, that's the last slide. Okay.

Pnina Mor: Okay, thank you.

Dr. Naama Srebn...: One last about the safety. If we gave estrogen only replacement, we even decrease the risk of breast cancer compared to estrogen and progesterone. And this is why we need to consider hysterectomy during the operation. Because of the easier way to treat the hormonal replacement therapy, we'll need estrogen only, and this is something that needs to be discussed with the patient around the operation. Thank you. Sorry for...

Pnina Mor: Okay. Okay, thank you very much. It was amazing, very informative. We do have a lot of questions. I'll try to choose between the different questions and we will

start. Let me see, hold on a minute. I think there's a question to Dr. Michaelson, hold on a minute. First of all, someone asked, what's the plan for including men in population testing? That's one issue. And are surrogates covered in Israel for BRCA patients? I don't know who that's for exactly. So if you want to address that in a few minutes, because this webinar ends at 9:00 and I want to get in as many questions as possible.

Dr. Rachel Mich...: Okay. So I'll answer the first question and maybe Naama will take the second one.

So we actually did a study on screening men, which was less complicated in the beginning than screening women because there are cancer risks for BRCA positive men, but their risks are much lower. Obviously, they won't get ovarian cancer. They do have an elevated risk of breast cancer, which is possible in men. And there's also a slightly elevated risk of prostate cancer among several other cancers, gastric and melanoma and others.

However, the absolute risk for men is lower. So it would be a little bit harder to actually prove that it would be cost-effective in men to screen a population. It could be that eventually we will get around to doing that. But right now, men are tested if they have a familial history or if there's a known genetic mutation in the family, just like women, were entitled to testing till now, according to those categories, it is possible that it will happen eventually.

Pnina Mor: Okay, thank you. Before we go to Naama, to answer that question to something else, I think it's for you. Somebody wrote, first, young woman had repeated tests for BRCA, came up negative despite family history, eventually after diagnosed with cancer, she did test positive so should some with a confirmed family history of cancer and BRCA gene in the family who initially tested negative be retested. If so, when?

Dr. Rachel Mich...: Okay, another great question. So I discussed population screening, and I mostly address women that have a low risk of having a genetic mutation. But don't forget women that have a high family history, a high risk according to their family history, must go through genetic counseling. And that's because just testing for the very common Ashkenazi Jewish BRCA mutations will not always cover them. Meaning it's possible to have what's called a private mutation, which means a mutation that is very rare in the general population and is not something that we're going to screen everyone for or test everyone for. But we might do a full sequence of the BRCA genes or even a gene panel, which is something that we send women to after having counseling. So if there's a family history that's suggestive of a genetic mutation, it's not enough to go through screening and you must go through genetic counseling.

Pnina Mor: Thank you. I'm going to skip some of the questions, and there's one question for Dr. Sella. Can you talk shortly about side effects of CDK4/6 inhibitors for breast cancer and why compliance with treatment is so low?

Dr. Tal Sella: Sure. First part of question.

Pnina Mor: That's a whole presentation.

Dr. Tal Sella: Sorry?

Pnina Mor: That's a whole presentation.

Dr. Tal Sella: Yeah, yeah, that's a lot. But I'll try to give you the headlines. So first part of the question, we have two CDK inhibitors that currently are available. One is abemaciclib. It's two years of treatment for that one. The main side effects are fatigue and gastrointestinal issues, abdominal pain and diarrhea is one of the things that we often encounter.

The other CDK4/6 inhibitor is called ribociclib, and that one is given for three years. No GI issues, fatigue, a little bit more of a complicated drug when it comes to interactions with other drugs, has more effects on blood counts. So sometimes a decreased white blood cell count, can increase liver enzymes and can cause some changes in the EKG. So a little bit more monitoring with ribociclib.

But we really are able to give both. Adherence is an issue with adjuvant therapy, in general, with hormonal therapy, we know is tough, oral medication that is given for five to 10 years. And we know that not most, but a significant minority of women do discontinue treatment at some point, and there are multiple reasons. I think the most common reason is of course, side effects. Another important reason, especially for the younger population, which I treat, is fertility. Women who want to have children, they can't do that while they're on treatment, so they stop. And today we have a lot of knowledge and experience in helping young women get pregnant and complete their fertility plan while also having a good oncology treatment plan. Of course, you don't do the things together, but you do one, you do the other, you go back to the treatment. There are different ways of doing these things. So fertility is another reason.

Pnina Mor: Thank you.

Dr. Tal Sella: Sometimes forgetfulness, there's a lot of issues.

Pnina Mor: Okay, thank you. And now there are a lot of questions that are for Dr. Srebnik. First of all, but it has to be very short because we're really supposed to end it now. But if everybody agrees, then we'll continue for a few more minutes.

Question, is there a study in Israel showing the safety of just removing tubes and not ovaries at 40? That's one. HRT, is it ever given after breast cancer, or anyone who has estrogen and positive breast cancer? There's two questions I put together. I know both questions are topics for a whole presentation, maybe we'll do it another time, but just very, very quickly answer.

Dr. Naama Srebn...: Okay. First, there is no surrogacy. It's allowed in Israel, but it's not covered. About HRT after breast cancer, it's very complicated. In specific cases of triple negative or VCIS, we can talk about it with oncologists and see if it fits, and then we can give hormonal treatment, but it's not the bread and butter. And there was a middle question. I forgot it.

Pnina Mor: It's basically the same. Tubes, HRT after breast cancer.

Dr. Naama Srebn...: Oh, tubes, yeah. There's no study in Israel. There are studies in Europe. They don't have results yet. So this is why in Israel, we do not usually do this procedure because we are not a part of any study right now. Once we'll have results, we'll let you know.

Pnina Mor: Okay, okay. First of all, thank you very much to everyone, and as we wrap up, I want to ask you to take a moment to fill a brief evaluation survey that is in the chat. And I want to tell you that there are several programs planned for the coming weeks. One in particular would be that I'd like to highlight is this coming Wednesday, February the 26th at 8:00 PM Israeli time, 1:00 PM Eastern Time, consider joining us for your anti-cancer morning routine with the nutritionist Rachel Beller.

Again, please remember that Sharsheret is here for you and your loved ones in the US and in Israel. Sharsheret provides emotional support, mental health counseling, and other programs designed to help you navigate the cancer experience and genetic questions that you may have. All are completely free of charge, completely confidential. Our contact information is in the chat box now.

Again, the evaluation link is in the box. Please fill it out and thank you for joining us tonight. Thank you all. It was really nice.