

Breast Cancer And Ovarian Cancer: Exploring The Connection

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Presented By:



Linking Young Jewish Women in Their Fight Against Breast Cancer

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I. Introduction

Elana Silber: Good evening. I'm Elana Silber, Director of Operations at Sharsheret. Thank you for joining us as we present the conference, "Breast Cancer and Ovarian Cancer: Exploring the Connection."

I would like to begin by thanking the North Jersey Affiliate of the Susan G. Komen Breast Cancer Foundation for their very generous support that enabled us to present this evening's conference. Sharsheret's staff and volunteers are the energy behind every Sharsheret event. And in particular, I would like to recognize Debra Wenger, Sharsheret Volunteer, Shera Dubitsky, our Link Program Coordinator, and Ellen Kleinhaus, our Program Coordinator, who organized this remarkable event and so many others.

Their contributions to the women of Sharsheret cannot be measured. Since Sharsheret's founding five years ago, we have received hundreds of phone calls and emails from women and their families concerned about hereditary cancer. More and more women are opting for genetic testing for BRCA1 and BRCA2 gene mutations with the knowledge that breast cancer survivors with a BRCA mutation are at increased risk of also developing ovarian cancer. Women are now calling Sharsheret with new concerns and treatment decisions relating to ovarian cancer. Their questions include: How are breast cancer and ovarian cancer related? What should I be doing to prevent ovarian cancer, now that I no longer have breast cancer? What measures should I take to prevent breast cancer, now that I have been diagnosed with ovarian cancer? I am concerned about developing ovarian cancer. May I speak with another breast cancer survivor who has tested for the gene mutations?

Our speakers tonight have generously contributed their time to address these important questions and more. We will hear brief presentations from each speaker, and then take questions from the audience. Our goal tonight is to answer some of your critical questions, and provide you with important facts that can help you make well informed decisions.

As with each of our medical conferences, this is the first of what is certain to be an ongoing conversation, and we encourage you to stay involved as the Sharsheret, the chain, continues to grow in the years ahead.

It's now my pleasure to introduce Dr. Noah Kauff. Dr. Kauff is a gynecologist and a geneticist at Memorial Sloan-Kettering Cancer Center. He specializes in the care of patients who may have an inherited predisposition to cancer. Dr. Kauff's research interests include the effect of genetic counseling on the evaluation and treatment of women with an inherited predisposition to cancer, the effect of risk reducing surgery for the prevention of breast and ovarian cancer in women with

an inherited predisposition to these cancers, and the identification of genetic and environmental markers that may allow risk reduction strategies to be tailored to individual patients at increased risk for cancer.

Please join me in welcoming Dr. Noah Kauff.

II. Presentation by Noah Kauff, M.D.

Dr. Noah Kauff: I want to thank Elana for the opportunity to come and talk with all of you today. And actually, I think a lot of what I'm going to do is really give an introduction as to what is the link between breast and ovarian cancer, and who should we be concerned about who may personally have breast or ovarian cancer, either themselves or the family members. Who should we be considering genetic counseling and testing to see whether or not these diseases are linked in an individual or in a family? Dr. Poynor is then going to talk a little bit about actually the management, once we've identified someone at risk. I'm going to defer most of the management issues to Elizabeth. And then, following that, Shera is going to talk a little bit about the process of genetic counseling and testing, and some of the impact that that can have as well on psychological issues.

In terms of why we're talking about inherited cancers, the most common cancers in women, as you see from the slide there will be about 216,000 cases of breast cancer diagnosed in this country this year. Of that, about 7 to 10%, or somewhere between about 15 to 22,000, are going to be the result of inheritable genetic predispositions. Additionally, of the 26,000 cases of ovarian cancer being diagnosed in this country, almost 10%, or somewhat over 2,500, will actually be the result of inheritable single gene predispositions.

The question is how do we find this 7 to 10% of women who may be at risk for one of these inherited predispositions. This is where the mainstay of identification is generally the family history. Things which make us suspect an inherited predisposition to cancer are: 1) If we see early age of diagnosis of particular cancers - when we talk about breast cancer, generally prior to the age of 50. 2) If we see cancer in two or more close relatives in the same family who have breast cancer or breast and related cancers, if we see a combination of cancers breast and ovarian cancer [in an] individual. There are some other syndromes, for example, uterine and colon cancer are actually into another syndrome called HNPCC (Hereditary Nonpolyposis Colorectal Cancer). 3) If we see multiple rare cancers within a family. For example, if we have multiple cases of pancreatic cancer in the setting of a history of breast cancer, that actually may be suspicious for a BRCA2 mutation as well. If there's any individual has multiple primary tumors. For example, someone with a personal family history of breast cancer, and then a second breast cancer - and that's individual.

If you look at these three family trees, which illustrate the types of family histories that we see, breast cancer is the single most common cancer in women. About one in nine women will develop it by the age of 85. It's a disease primarily of the 60s, 70s, and 80s. If you look at the family tree on the left, in the grandparents'

generation there is a single breast cancer in a woman at 65. No other cases of breast or ovarian cancer. This is almost certainly a sporadic cancer. The single biggest, or the two single biggest risk factors in the development of breast cancer are: number one, being a woman and number two, getting older.

In the family tree on the right you see breast cancer at 42 in the grandparents' generation, breast cancer at 38 and 46 in the grandchildren's generation, and in the generation between, ovarian cancer at 56. That is not a family you need a geneticist to say that something is going on in this family. Where I think genetic counseling and testing can help us the most is actually the family in the middle, where we see two cases of breast cancer, both in the early 50s. This is where we begin to be concerned about the setting of an inherited predisposition. Are we seeing the cancers more frequently than expected and at earlier ages than expected? Clearly in the family on the right, we are. The family on the left, we're not. Where genetic counseling and testing I think can help us most is that family in the middle, to help us figure out, is this something which we have to be worried about a link between breast and other related cancers?

The hallmarks of inherited cancer syndromes are that we see the cancers at earlier ages than expected and more frequently than expected. Why is that the case? Well, as Elana mentioned, obviously, we're going to be talking a lot about BRCA1 and BRCA2, which are the genes which are associated with an inherited predisposition of breast and ovarian cancer. You'll sometimes actually hear people say, I've inherited the gene. That's actually a misnomer. All of us have two copies of BRCA1 and two copies of BRCA2. What they do when they're working properly is check on cell growth and actually prevent cancers from developing. They're what we call tumor suppressor genes. We each have two copies of BRCA1, one which we got from our mother and one which we got from our father. Similarly, for BRCA2, we have two copies. They work as brakes on cell growth like two sets of brakes on a car. Because Mother Nature is good to us, we only need one set of these brakes to be working in order for cancer not to develop through a defect in this mechanism. What has to happen in order for cancer to develop through a defective BRCA1 pathway is that we have to lose, in an individual breast or ovarian cancer cell, both working copies of BRCA1 or BRCA2. What you can see happens is in someone who does not have an inherited mutation, as our breast cells divide or as our ovarian cells divide, in the cell division, a mutation can occur that knocks out one working copy. As long as the second working copy is there, cancer does not develop through this pathway. It's only if in a subsequent cell division of one of those daughter cells does the cancer actually develop.

However, for people who have inherited a BRCA mutation from either their mother or their father, what has happened is they have inherited, in every cell of their body, a defective copy of either BRCA1 or BRCA2. What has to happen is that a breast or ovarian cell just has to lose that second copy for cancer to

develop in this pathway. This is why, since every cell in the body is one step closer to developing cancer, we see the cancers both earlier than expected and more frequently than expected.

The thing which is important is that if you've inherited a mutation it doesn't mean that you will develop cancer. It substantially increases the risk. But what may happen is one of the tissues at risk may never develop a second mutation or that second hit. Things that can modify this are certainly exposure to carcinogens, exposure to hormonal or environmental factors, reproductive factors, as well as modifier genes that we've not yet identified. It's important to remember that a mutation of one of these genes does not make cancer a certainty. We have to then say, what can we do to modify that risk to prevent that second hit from occurring?

This is an example of a family history which is characteristic or classic for a family which has a BRCA1 mutation. In this family you see that in the children's generation there is breast cancer at 38 and ovarian cancer at 45. The next generation up you see two breast cancer diagnoses, one in the 40s, one in the 50s. And in the generation above it, importantly, the grandmother, who is the matriarch of this family, is 62. She actually had the mutation, but died of a heart attack at 62 - never developed breast or ovarian cancer. Interestingly, she has a daughter who has the mutation and got to 78 and never developed breast or ovarian cancer. But, her daughter did develop ovarian cancer at 45. Additionally, these can be transmitted through men. Particularly when you're looking at family histories, if you have small families, which there are not many women in it, because the cancers predominantly do not affect men, you have to be a little bit careful not to assume that we're not dealing with an inherited predisposition just if we've got, for example, a very early age of onset of breast cancer.

In terms of genetic counseling and testing we use the family history to just determine: who we should be evaluating and considering for molecular genetic testing, who should see a cancer genetic counselor or other cancer professional, who we should be offering genetic testing, and once we have identified someone at risk, what we can do for screening or other risk reduction.

BRCA1 and BRCA2 were only identified in 1994 and 1995. When we actually started offering genetic counseling and testing about a decade ago, it wasn't clear that we could actually do anything after we've identified an individual at risk. What we have learned in the last 10 years is a great deal about the natural history of the disease, but more importantly, that we can alter the natural history of the disease. And now, the development of cancer is not a high likelihood or a certainty, but with appropriate risk reduction, we actually think it's in many cases more likely that individuals at risk will not develop cancer.

A couple of things, when we're looking at family history that you'll want to keep in mind. The family history, particularly once we get beyond our very close relatives, our parents, our siblings, and our children. It's not surprising if you don't know what your grandmother or your aunt actually had for their cancer diagnosis. In this particular example, the grandmother's stomach cancer turned out to be an ovarian cancer at 48. The person who had liver cancer was actually breast cancer, which metastasized to the liver. When we're doing a hereditary cancer assessment, what is important in determining inherited risk is where the cancers start, not where it metastasizes to. Sometimes it's going to require making phone calls, speaking to other relatives who were closer to the individual, getting pathology records - because it can help clarify and say we are at increased risk. Or interestingly, I have some patients who come to me and say my grandmother and my aunt had ovarian cancer. When they tell me the story and the history it just doesn't make sense. Before we start doing intensive risk reduction let's get some records, let's make sure that's actually what we're dealing with. Because what you've just described to me doesn't sound like ovarian cancer. It turns out that people may not be at risk. It's very important to verify the history.

The other thing to remember is your own individual history. Many of you in this room have actually already had a breast cancer or an ovarian cancer. You may have in fact been the first one in your family diagnosed. As I said, if you have breast cancer in your 60s, in and of itself it's not particularly suspicious, but your family history changes. It may have been when you met your doctor and you had your breast cancer in your 60s, the family history was not suspicious. But then, your niece through your brother developed breast cancer in their 40s two years from now. This is when it sometimes is necessary to reassess. The genetic history which your doctor takes is a point in time. It's important that you let your doctors be aware of new cancers that may have occurred since you've last spoken about your family history.

There are some limitations to family history assessment - small families. If there are not a lot of individuals in the family, you can't see five or six people with breast or ovarian cancer. If you're an only child, your parents were only children, if there are very few women in the family - because most of hereditary breast or ovarian cancer only affects women, and if you're adopted, you may not know the family history.

The other thing which we sometimes actually have to think about is non-paternity, believe it or not. Something which I know does not happen to anyone in this room, but actually in studies which I've looked at, about 6% of all people in this country's father is not who they think it is. You have to be a little bit cautious. It's something which we think about as geneticists.

This is a slide which shows clearly inherited breast cancers. If you have multiple

generations all with early onset breast cancer - four or five, six patients - all with early onset breast cancer. How often is this actually caused by BRCA1 or BRCA2 even in the clearly inherited cases? The thing which is actually important is just over 50% of the time. That is quite important because if you've had genetic testing and we don't find a mutation doesn't mean there's not an inherited predisposition. In the setting of a very strong family history - no. In that situation we have to take care of you based on the family history. In the setting of a family history that's not particularly strong it's actually reassuring. In the setting of a very strong family history we know there must be other genes that cause inherited breast cancer, but we've not been smart enough to identify them as of yet.

One thing which is some preliminary data that we put together last year, looking at the risk of ovarian cancer in women in families who had a very strong family history of breast cancer and fortunately no ovarian cancer who were BRCA negative. We looked at how likely individuals in these families were going to develop ovarian cancer. It turned out there was no difference from what we saw in terms of the expected rate of ovarian cancer than what would have been expected in the general population. This is the first study of its type and so it still needs to be replicated. It may suggest that for the women who are BRCA negative, who come from a very strong family history of breast cancer, they may not be at an increased risk of ovarian cancer.

We're talking about BRCA1 and BRCA2. Both of these genes are what we call tumor suppressor genes. They happen to be located on chromosome 13 and 17. What they do, as I mentioned to you, is they prevent cancers from developing when they're working properly. Although we talk about BRCA1 and BRCA2 in the same breath, they are actually two related but distinct cancer susceptibility syndromes. Both are associated with a very high incidence of breast cancer. For BRCA1 mutation carriers about a 50 to 85% lifetime risk of breast cancer. Importantly, the breast cancers can start as early as the mid-20s. About half of the women with a BRCA1 mutation will actually develop breast cancer by the time they are 50. In terms of a second primary breast cancer, it is about one out of two women with a BRCA mutation will actually develop a breast cancer, on the other side, in their lifetime. That's one of the reasons why it's important for people who are saying, "I've already had breast cancer. Why do I need to do something differently?" It's because of that risk of second breast cancer. Additionally, up to about 40% or so of women with one of these mutations will develop ovarian cancer.

BRCA2 is similar. Again, it has a 50 to 85% lifetime risk of breast cancer. These are the risks if we don't do anything to prevent it. This is where Dr. Poyner is going to talk about some of the risk reduction strategies that are available. Again, the breast cancer risk can be very early onset, as early as the 20s. Ovarian cancer risk is still substantially greater than the general population

whose lifetime risk of ovarian cancer is about 1.5%. In the setting of a BRCA2 mutation, it's about 10 to 27%. But importantly, the risk of ovarian cancer is predominantly postmenopausal. This is going to have important implications as we talk about timing of risk reduction. In addition, there's probably a three to five-fold increased incidence of prostate cancer for men who have BRCA2 mutations. There's about a 100-fold increased incidence of the risk of male breast cancer. About one out of 20 men who have a BRCA2 mutation will develop breast cancer in their lifetime. And it is something which does need to be addressed for the men in these families.

How common are these? In the general population we see these mutations about one in 400 to one in 800 individuals. BRCA mutations have been seen in all racial and ethnic groups and in all populations. If we look at the entire U.S. population, as I said, it's about one in 400 to one in 800 individuals will have one of these mutations. However, the Eastern European Jewish population, which does represent close to 90% of Jews in the United States, it is about 10 times more common. We see it in about one in 40 Eastern European Jews. The reason we see this is actually the result of a random genetic event called a founder effect. And we can see this in any population which is reproductively isolated for geographic or other reasons. There are several mutations, there are actually three very specific mutations, that have been described in the Eastern European Jewish population, which are called founder mutations.

If you take any one of them, the most common one is a mutation of BRCA2 called 6174 del T. That mutation occurred about 500 years ago and it occurred in a single individual. It was a random genetic event. The descendants of that individual were living in certain villages. But it turned out the Eastern European Jewish population went through a period where around the birth of Christ the population of Jews was about 4.5 million. During the Middle Ages it dropped to about 10 to 20,000. It re-expanded just prior to World War II to about 16 million. The direct descendants of that individual happened to live in villages, which during famine got more food, when the Black Plague came through, they didn't see a lot of it and when various invading armies missed those villages. It wasn't that the mutations were protected, it just happened to be the people who were direct descendants of this individual were in villages--preferentially survived. When the Eastern European Jewish population expanded, the descendants basically became overrepresented in the Eastern European Jewish population. Although one out of 100 Eastern European Jews has this particular 6174 del T mutation, fundamentally, every one of those individuals is a direct descendant of this single individual who lived about 500 years ago.

This [slide] is just a graphic which shows, as I mentioned, the Jewish population was about 4.5 million around the time of the birth of Christ. It dropped to less than 10,000 through the Middle Ages, and then re-expanded over the last 500 to 600 years. The descendants of these three founders ended up being

overrepresented. Founder mutations are actually not unique to Eastern European Jews. There have been founder mutations described in at least a dozen different populations. You see in addition to the Eastern European Jewish population: Icelandic, Finnish, Norwegian, Dutch, and French Canadian populations. All of these share that feature that these were populations that were reproductively or geographically isolated and went through marked population contractions and then subsequent expansions.

I have now just said that one out of 40 women of Eastern European Jewish heritage has one of these mutations. If that's the case, if you have breast cancer, if you have ovarian cancer, what does this mean for you, if you've got a much higher likelihood of starting with the BRCA1 or BRCA2 mutation? If we take women who have breast cancer at less than 40, about 10% will actually have a BRCA1 or BRCA2 mutation. However, if you're of Eastern European Jewish heritage and have breast cancer prior to 40, that actually increases to one out of four. If you have ovarian cancer at any age and are not selected for ethnicity, somewhere between 8 and 13% of women will have a BRCA1 or BRCA2 mutation, as opposed to if you are of Eastern European Jewish heritage, one out of three. Given that, even in the absence of any family history, a family history of early onset breast cancer, even prior to 50, a history of ovarian cancer at any age--it does not have to be early, and the Eastern European Jewish heritage, is in my mind enough reason that we should be offering genetic counseling and testing. Hopefully, that will be the standard of care in the very near future.

This is just a summary slide of looking at who should be considered for hereditary cancer risk assessment. For individuals who are not of Eastern European Jewish heritage: if they've had breast cancer at less than 40, if they have had breast cancer at less than 50 and someone else in the family has breast cancer also less than 50, if there's breast cancer less than 50 and ovarian cancer at any age, or if there are more than three breast cancers in the family at any age. Additionally, some people argue and I tend to agree, but I am a geneticist, that any woman with ovarian cancer should be offered the opportunity for genetic counseling and testing. For women of Eastern European Jewish heritage, I think, any woman of Eastern European Jewish heritage who has breast cancer at less than 50 should be offered genetic counseling and testing, or someone who has breast cancer older than 50 and there is any close relative with a breast or ovarian cancer in the family.

Since one out of three women who are Jewish and have ovarian cancer have a BRCA1 or BRCA2 mutation, I think it's something which we need to be offering to all Eastern European Jews who have ovarian cancer. And the other reason why that's important is people might say, well, I have ovarian cancer. Obviously, we know ovarian cancer is a lethal disease. However, there are people saying, well, why do I need to do breast cancer screening? Let's say I have no female relatives. I don't have any children. Is there anything that's going to impact me?

Well, there are a couple of things which it might impact. It turns out that there are now five studies which have shown that BRCA-associated ovarian cancer is associated with substantially improved survival compared to sporadic ovarian cancer. The reason that that seems to be the case is that the same defect that leads to the development of the tumor also makes the ovarian cancer exquisitely sensitive to chemotherapy, so just that it is the rule, not the exception, to be a long-term survivor after ovarian cancer, if you are dealing with a BRCA-associated ovarian cancer. We want to make sure that breast cancer doesn't pop up into the picture. The second thing, and we're not there yet, but in the very near future, in the next two to three years, the first human trials are occurring right now in England are looking at agents for tumors that are developing because of a defect in the BRCA pathway, to use particular chemotherapies for the treatment of recurrence. We know that BRCA mutations are an extremely important prognostic factor for ovarian cancer. It's something which we're beginning to think about - how can we use this to better treat it. It's something which may in fact even have a direct role in therapy.

In terms of what are the risk reduction strategies, basically, they center on three approaches. One is what we call secondary prevention, which is the detection of cancer in its early, most treatable, and most curable stage. Then we have primary prevention approaches, which are chemoprevention, which are medications to prevent cancer. There is some data that suggests that that might be helpful for both breast and ovarian cancer. Then there are the risk reducing surgical approaches.

I'm going to leave that part to Dr. Poynor, and I look forward to your questions afterwards.

Elana Silber: Thank you, Dr. Kauff. It is now my pleasure to introduce Dr. Elizabeth Poynor. Dr. Poynor is a gynecologic oncologist and pelvic surgeon who focuses on the comprehensive surgical management of gynecologic cancers and works with medical and radiation oncologists to facilitate a compassionate multidisciplinary approach to the management of women's cancers. She has a special expertise in the complex management of women and their families who have a genetic predisposition to developing breast cancer and gynecologic malignancies. As a surgeon scientist, Dr. Poynor's work focused on translating basic science principles into clinically meaningful treatments and she served as Director of Translational Research for the Gynecology Service at Memorial Sloan-Kettering Cancer Center. She has also served as an investigator in numerous clinical trials relating to surgical, medical, and biological treatment of gynecologic cancers. It is now my pleasure to introduce Dr. Poynor.

III. Presentation by Elizabeth Poynor, M.D., Ph.D., FACOG

Dr. Elizabeth Poynor: And now, I'm just in private practice taking care of patients and enjoying it. Thank you for inviting me to speak this evening. This is one of the special focuses of my practice. And thank you to Noah for really describing the genetic links between breast and ovarian cancer and really defining women who are at elevated risk to develop these diseases. Now that Noah has discussed the genetic links between these two cancers, I'd like to get into the management and how we can reduce the risk of developing one of these cancers in women who may be at elevated risk, and also review screening principles to detect the diseases at their earliest stages where they're typically the most curable. I'll be discussing, in relationship to both breast and ovarian cancer, screening techniques to detect the tumors at earlier stages, chemoprevention strategies in order to prevent tumors from developing through treating healthy women with medications in order for prevention, and also to discuss prophylactic surgery, which refers to the removal of a healthy organ to prevent disease occurrence.

A woman can be defined to be at elevated risk to develop breast or ovarian cancer based on her family history. If she's a member of a hereditary breast and ovarian cancer kindred, if she's had genetic testing, which demonstrates her to carry a mutated BRCA1 or BRCA2 gene, if she has a diagnosis of breast cancer she may be at elevated risk to develop ovarian cancer depending on her age of diagnosis of breast cancer. Also, a woman who has developed ovarian cancer has at least a two-fold elevated risk to develop breast cancer in her lifetime. This may be more significantly elevated if she has a mutation in a cancer predisposition gene.

Just to review the basics of screening strategies, screening is defined as the application of a test to identify individuals at risk of a specific disease which would benefit from further investigation or prevention - a preventative action. One of the purposes of screening is to identify a disease in its earliest stages. Stage for stage, stage one solid tumors, either breast cancer, ovarian cancer, or colorectal cancer, generally, the survival rates are in the 90% range. When you go down to stage three or four cancers, those survival rates decrease down into the 25% range. That's a general principal for any solid tumor. It is also important that the screening test be simple and safe. It must be well accepted by an individual. It also must be cost effective and have an adequate detection rate in order to be an acceptable screening test. This has been defined by the World Health Organization.

In summary, for ovarian cancer, there is not a well accepted screening test, unfortunately. There is not a test yet that meets these criteria established by the World Health Organization. So, in general, we don't screen women for ovarian cancer in the general population. The screening strategies which are used

currently for the early detection or attempted early detection of ovarian cancer, include a pelvic examination every six months combined with a tumor marker called a CA125, which lacks the appropriate sensitivity and specificity to be a good screening marker for ovarian cancer. This is also combined with transvaginal ultrasound, which unfortunately despite a number of cogitations that we've done with ultrasounds, lacks the specificity, and also probably does lack sensitivity in order to be an effective screening strategy.

CA125 for screening can be elevated with other cancers other than ovarian cancer. CA125 can be elevated with breast cancer, colon cancer, pancreas, or lung cancer. It is also elevated with benign conditions, so it lacks that specificity that we need for a good tumor marker. It can be elevated with fibroids, endometriosis, liver disease, cardiac disease - any inflammation basically of a peritoneal surface. There is a need for new markers. I'll briefly discuss proteomics, but this is a new technique that's come into the forefront over the past four or five years where we're actually searching for new tumor markers in the blood of affected individuals in order to come up with better tumor markers to screen for ovarian cancer.

This slide demonstrates to you that CA125 not only lacks specificity, but it also lacks sensitivity for the early detection of ovarian cancer. To have an impact on decreasing the mortality from ovarian cancer, we have to be able to pick up the disease at an earlier stage. We have to be able to pick up stage one disease. And unfortunately, CA125 only is elevated in approximately 50% of individuals with stage one disease. Where we want to detect it, the CA125 is not significantly elevated in a significant proportion of individuals.

This [slide] demonstrates the use of transvaginal ultrasonography for screening for ovarian cancer. And the positive predictive value or that number of tests which are positive, which actually turn out to be positive on further investigation, which by the World Health Organization criteria should be at 10% - so that out of every 100 operations, you should at least find 10 ovarian cancers based on a positive screen – here it shows only 3%. The ultrasound screening for ovarian cancer lacks the specificity. And again, we do a bunch of cogitations where we look at the type of cyst that's in the ovary. Does it have a septation in it? Does it have a thick septation? Does it have solid areas? Even with that we can't increase the positive predictive value. Investigators are now combining CA125 and ultrasonography.

There is a group in England, which is using a risk of ovarian cancer protocol that was developed in the United States, is looking at the rate of rise of CA125 over time combined with ultrasound. That had some early preliminary findings, that people were quite enthusiastic about and that maybe these investigators were able to pick up ovarian cancer at an earlier stage. However, the overall mortality from ovarian cancer or that gold standard test for a screening test actually was

not met in those early studies. Those studies are ongoing in the United States and England currently. But right now, there's not a well accepted screening test, unfortunately, for ovarian cancer.

Other new technologies which individuals are looking at are proteomics. It is basically a protein signature in a woman's blood. What investigators do is they draw blood from individuals who have cancer and don't have cancer. They look at the protein signatures or the proteins in the blood of these women, or fragments of proteins, and they look for what proteins are present or if they could come up with a fingerprint of a pattern of proteins in women who have ovarian cancer. Early studies in these technologies were very promising. It's a very tricky technique associated with many nuances. Studies are ongoing throughout the United States with proteomics, but we're not there yet.

This slide demonstrates to you (this is actually from one of my patients) that I don't know that an effective screening technology for ovarian cancer is actually ever going to exist. This is a prophylactic oophorectomy specimen from an individual who had a BRCA1 or 2 mutation. Ovarian cancer arises from the surface cells covering the ovary. These dark cells on the right-hand panel that you're looking at that are stained dark brown or black are actually tumor cells. You can see that there's just a cluster of about 500 cells in that ovary that were actually beginning to become cancer. That shows that there's a few number of cells that are already breaking off. It may be very, very difficult to ever develop an adequate screening technology for ovarian cancer. That is what makes prophylactic surgery very important in the prevention of this disease.

It is also important as clinicians and also as patients that you all are aware of the early warning signs and symptoms of ovarian cancer. Typically, early warning signs and symptoms can be urinary frequency, bloating - which is unusual - pelvic cramping, or just a different feeling in your pelvis. Unfortunately, these symptoms are associated with a number of other very common situations that a woman can face. But anytime the symptoms are persistent or getting worse, they need to be evaluated aggressively with a transvaginal ultrasound or a CT scan. And I think individuals need to be proactive in that portion of their health care because not every internist is going to pay attention to those symptoms the same way.

The next approach in addition to screening is to try to prevent the disease from occurring. Chemoprevention is the use of medication to lower the risk of a cancer in a healthy person. Oral contraceptives have been known as effective chemopreventive agents in ovarian cancer for a long time. Overall, there's a 60% risk reduction of ovarian cancer in a woman who has taken oral contraceptives for six years or greater. This risk reduction seems to translate in observational studies in individuals who have a BRCA1 or BRCA2 gene mutation. We see the greatest effects in this population in a similar fashion after

six years of usage. However, additional research is required to further quantify that risk reduction. New techniques for chemoprevention of ovarian cancer include analgesics, nonsteroidal anti-inflammatory drugs, Tylenol, and aspirin. There are a number of conflicting studies, some of which demonstrate that there is a risk associated with the use of these types of analgesics in ovarian cancer. For each one that shows that there is a risk reduction, there is also one that shows that there isn't. It's somewhat controversial. Fenretinide is also a drug which is related to Vitamin A, which is a differentiating agent, which is being studied currently in ovarian cancer with chemo prevention. However, that data is not available yet.

For the highest of risk individuals we will also discuss prophylactic surgery in order to prevent the development of ovarian cancer. Candidates for prophylactic surgery, or removal of the tubes and ovaries, include individuals with a documented BRCA1 or BRCA2 mutation, members of an HNPPC family or Lynch family in which colorectal cancers, endometrial cancers, ovarian cancers, and other GI tumors travel in that family. These individuals usually also undergo a prophylactic hysterectomy, as well, because they are at significantly elevated risk to develop endometrial cancer. Individuals who are members of families in which you see a hereditary pattern of breast and ovarian cancer who test negative for BRCA1 or 2 mutations, which accounts for approximately 15% of hereditary breast and ovarian cancer families, are also counseled concerning prophylactic surgery. Or if an individual has two or more first degree relatives with ovarian cancer, we'll also talk to her about undergoing prophylactic removal of the ovaries.

The age which we begin to discuss prophylactic surgery is after childbearing is complete or before the completion of the fourth decade of life, before you reach the age of 40. You see in that red line on the top [slide], those are individuals with BRCA1 mutations and the age at which they begin to develop ovarian cancer. You see that that begins to take off between 30 and 35 that we see the risk for ovarian cancer begin to go up. It is later for individuals with BRCA2 mutations. Women with a BRCA2 mutation are more at a population risk, or a little bit later in life risk, for development of ovarian cancer. That may have some bearing on when you recommend prophylactic surgery to an individual who has BRCA2 mutation. But I always tell people, "Don't take great solace in that because you need to look at the youngest age of the individual who developed ovarian cancer in your family, and you need to definitely get your surgery done before that and maybe even 10 years before that." There is something called "anticipation in genetics" that we see in families in which each generation may develop cancer at an earlier age. Certainly you need to interpret this in reference to the family history and the ages at which ovarian cancers developed in the families.

I typically do this surgery now through three ports. We have a 10-millimeter port

that goes right into the bellybutton, so you never see that scar. There are two 5-millimeter ports on the right and the left sides that go into the abdomen. This is all done through laparoscopy, minimally invasive surgery. We can get an excellent look throughout the abdomen. We can biopsy any other peritoneal surfaces that we need to through this technology. You see the uterus. The ovary is behind the fallopian tube, the fallopian tube on the right. We take the blood supply to the fallopian tube and the ovary. We also take great effort to remove as much of the fallopian tube as possible and burn the little end of the fallopian tube because individuals with a BRCA mutation are at elevated risk to develop a fallopian tube cancer. It's important to get rid of as much of that fallopian tube as possible. This data actually comes from Dr. Kauff's study at Memorial in which they found that there was a 95% reduction in gynecologic associated cancers in women who underwent prophylactic surgery.

For a long time the history of prophylactic surgery was: You took out the ovaries in individuals who were at high risk, but they were still at risk to develop primary peritoneal cancer, a cancer which is derived from the same type of cell that ovarian cancer is derived from, but it's not the cells covering the ovary, it's the cells lining the abdomen. This cancer is treated like ovarian cancer, acts biologically like ovarian cancer, and looks just like it underneath the microscope. Dr. Kauff was the individual who showed us that when he looked at individuals who had undergone prophylactic surgery, who were at elevated risk to develop ovarian cancer, that there was a significant decrease in the risk of associated gynecologic cancers. It is almost important to realize that prophylactic oophorectomy can decrease the risk of developing breast cancer in very high risk individuals by up to 68%.

There are risks of occult cancers in the fallopian tube and the ovary found at the time of prophylactic surgery. I showed you one of the very beginnings of one. It is very important that the surgery be performed by individuals who have knowledge of prophylactic surgery, who have a dialogue with their pathologist. The pathology specimens actually are not sectioned as a typical pathology specimen is. The pathologists actually take very careful attention to detail in sectioning the ovaries and fallopian tubes in these specimens that we send them to look for these occult cancers, so that individuals can be treated appropriately. There is still a risk of primary peritoneal cancer, so that you are not completely 100% protected against a cancer that looks and acts and is treated like ovarian cancer. But the overall risk of that in the highest of risk individuals seems to be in the range of 3%, quite low.

The side effects are very important to discuss with any individual considering prophylactic surgery because typically these are women that are premenopausal. Some individuals are postmenopausal by the time they get to their discussion concerning prophylactic surgery, but a surgically induced menopause can actually be a devastating situation for a younger individual. The question that

always arises in my office is: Can estrogen be utilized after prophylactic surgery? The answer to that is, yes, if you don't have a history of breast cancer. It's important to note that in a study of women who had BRCA mutations, those individuals who underwent prophylactic surgery and then took estrogen afterwards, were not at elevated risk to develop breast cancer. They kept that lower risk of developing breast cancer. By taking out the ovaries in a prophylactic fashion, the risk of breast cancer was cut by 50% and that was not negated by hormone replacement therapy.

Non-hormonal therapies are always discussed in individuals who have a history of breast cancer or who desire to avoid surgery. Of course, vitamins can be used to try to control hot flashes. There are a number of pharmaceutical agents, blood pressure lowering agents, CNS (Central Nervous System) acting agents, sedatives, which can also be used to control hot flashes. There are alternative therapies that we also discuss with our patients, including acupuncture, hypnosis. Soya agents are a little dicey. They're phytoestrogens and there's not a lot of good data on them and I use them with great caution because they are not well regulated in terms of the quality control. Of course, you have to pay attention to bone loss after surgically induced menopause also, but that can also be managed with pharmaceutical agents, including anti-resorptive agents.

In terms of the individual who is at elevated risk to develop breast cancer, we typically recommend mammography. I'll go over these recommendations in a minute. Ultrasound is currently under investigation in individuals who are at elevated risk to develop breast cancer. MRI has now moved from the research arena into a well accepted screening--as a well accepted screening strategy for individuals who are at elevated risk to develop breast cancer. Breast self examination is recommended to begin at 18 years on a monthly basis. It should be performed at the same time each month. Clinical breast examination is recommended to begin at the age of 25 years to be performed every six months to a year. That's typically performed by a health care professional. Mammography is also recommended to begin at the age of 25 years for the woman at highest of risk to develop breast cancer. However, mammography is not as sensitive in women who are younger and have dense breasts. MRI is now a well accepted screening strategy in individuals who are at elevated risk to begin at the age of 25 years. MRI has a higher sensitivity of detecting breast cancers. However, it also has a much higher false positive rate. So women undergo a number of biopsies which may turn out to be benign in that trade off to have a more sensitive screening strategy. Chemoprevention has been extensively studied for breast cancer prevention. Currently only one drug, Tamoxifen, is FDA-approved for chemoprevention. It's typically given to women who are at the highest of risk to develop breast cancer or who, through the Gail model, are at elevated risk to develop breast cancer, and it is given to women who are 35 and older to decrease the risk of developing breast cancer. There is currently ongoing research in terms of the application of aromatase inhibitors in

order to prevent breast cancer.

Tamoxifen is a member of a class of drug called a selective estrogen receptor modulator. These drugs actually affect the way the estrogen receptor works, so that they can't work on some tissues. Raloxifen is another type of a serum drug similar to Tamoxifen. And these drugs can either enhance the effect of estrogen in some tissues, like Tamoxifen in the uterus, or they can turn off the effects of estrogen and Raloxifen in the breasts. Aromatase inhibitors are another class of drugs which actually block the peripheral conversion of other hormones in the body, such as androgens, into estrogen. These are typically used only in postmenopausal women and are currently under investigation in the prevention role. These include: Arimidex, Aromasin and Femara, which I'm sure you've heard a lot about. Other drugs which are being brought into the chemoprevention strategies for breast cancer include non-steroidal anti-inflammatories similar to ovarian cancer--the data is not so clear cut - Deslorelin, which is a drug which turns off the ovary and cuts down on estrogen production, and Fenretinide, that Vitamin A-type drug. Tamoxifen results in a 75% decreased risk for contralateral breast cancer in affected BRCA carriers. Its use in BRCA1 mutation positive individuals is somewhat controversial because Tamoxifen turns off the effects of estrogen. But many of the tumors in BRCA1 affected individuals are actually ER/PR negative. In unaffected BRCA2 carriers, however, Tamoxifen results in a 62% decrease in the risk of developing breast cancer. In the unaffected high risk individuals, Tamoxifen overall - not separating out for whether you are mutation positive or not - leads to a 50% decreased risk for the development of breast cancer.

Prophylactic mastectomy has also been employed in the prevention strategy for breast cancer. Of course, a prophylactic mastectomy refers to the removal of healthy breasts to decrease a woman's risk of developing breast cancer. There is still a risk of 5 to 10% of developing breast cancer after a prophylactic mastectomy. The data is well accepted now that this decreased risk can be up to 95% in individuals who undergo an oophorectomy in addition to their prophylactic mastectomy.

There are a variety of types of mastectomies that are performed. Modified radical mastectomy refers to removal of the breasts and the axillary nodes. Simple mastectomy, which is the most effective type of mastectomy for prophylaxis, includes removing the breast and just the nodes in the just adjacent area. Skin sparing mastectomies and subcutaneous are mastectomies which leave more skin to facilitate reconstruction, however are less effective at preventing breast cancer. Subcutaneous and nipple sparing mastectomies actually spare the nipple. However, the nipple is not functional many times and sensation is not good. Many times with nipple sparing mastectomies you go on to have problems with the nipple. It's well accepted that simple mastectomies are the most effective prevention strategy for breast cancer. Sentinel node

mapping and axillary dissection is also a bit controversial. Some surgeons may talk to you about sentinel node mapping at the time of prophylactic mastectomy. But again, that is not well accepted and somewhat controversial. There is a greater than 90% risk reduction in individuals who have a documented BRCA1 or 2 mutation. Simple mastectomy is the most effective way to prevent breast cancer. Immediate reconstruction is also possible and also should be discussed in terms of tissue expanders or TRAM flaps and should be discussed with a plastic surgeon after a decision is made to go ahead with prophylactic surgery.

Women who are at elevated risk to develop ovarian cancer, we recommend increased surveillance, typically with a CA125 and an ultrasound every six months. We also talk to individuals about enrolling in screening protocols or research studies which are available in the area, oral contraceptives until child bearing is complete, prophylactic oophorectomy is also discussed after child bearing is complete, and if there is no personal history of breast cancer, hormone replacement therapy can be considered until the age of 50 after surgery.

Breast cancer screening recommendations increase surveillance in terms of interval and also application of new technology, such as MRI, consider chemoprevention strategies, which include Tamoxifen or enrollment again on research studies and consider prophylactic surgery. There are improved medical outcomes with proven medical interventions, such that a women's knowledge of her risk leads to power in terms of early detection and prevention of disease.

Elana Silber: Thank you Dr. Poynor. It is my pleasure to introduce Shera Dubitsky. Shera is Sharsheret's Link Program Coordinator. She served as a psychology resident and fellow at the Bronx Psychiatric Center of the Albert Einstein School of Medicine and as an Associate Psychologist for the Jewish Board of Family and Children Services. She has also worked as a researcher at Memorial Sloan-Kettering Cancer Center. As Sharsheret's Link Program Coordinator, she assists women newly diagnosed and at high risk of developing breast cancer and provides supportive counseling to women living with advanced breast cancer. Please join me in welcoming Shera.

IV. Presentation by Shera Dubitsky, M.Ed., M.A.

Shera Dubitsky, M.Ed., M.A.: First of all, I'd like to begin by dedicating my remarks this evening to the women who call into Sharsheret, because it's really through their wisdom that I get my education. What I'm going to be speaking about tonight really comes directly from the women that I'm working with.

While there is an ongoing debate as to whether breast and ovarian cancer rates are higher in Jewish women as compared to the general population, the proportion of breast and ovarian cancer that is hereditary is higher in the Jewish woman of Ashkenazi descent. There has been, however, a lot of media attention questioning what is the true risk of developing breast or ovarian cancer among women carrying the gene. The New York Breast Cancer Study found that among American Jewish women who trace their ancestry to Eastern Europe, those who carry the mutation in the BRCA gene have as high as an 82% chance of developing breast cancer by the time that they're 80. Now, critics say the genetic study may have overestimated the breast cancer risk. And the disagreement is whether the true risk is closer to 50% or to 80%.

And Dr. Wacholder of the National Cancer Institute points out that because when women learn through genetic testing that they have a BRCA mutation, they are choosing to have their breasts and ovaries surgically removed in hopes of staying cancer free, and that the true cancer risk posed by the mutation is no mere academic dispute. Life changing decisions are being based either on a 50% coin toss or a virtual sure thing at 80%.

On the heels of this debate, I wondered for the Jewish women calling Sharsheret already diagnosed with breast cancer, is the fear of recurrence of breast or ovarian cancer different than the fear of subsequently being diagnosed with another cancer? A frequent discussion I have with women who are newly diagnosed is: How does one go about making these life altering decisions in just a matter of days or weeks? After all, doctors go to medical school and they have internships and fellowships, and they specialize in the area of ovarian cancer, while a woman is expected to synthesize sometimes varying opinions and make decisions based on researching information all in a matter of days when doctors had years to learn this.

What I have found most striking about this are two things. One is, just how proficient women actually do become in the language and understanding of breast or ovarian cancer in such a short period of time. And two, that women are discovering their resiliency, courage, and strength also in a quick period of time.

Time and again I'm having conversations with women who are saying to me, "When I was first diagnosed I was thinking how am I ever going to find the

strength to get through this? And I did.” Then, it's time to do the treatment and women say, “How am I ever going to find the energy and the strength to tolerate the side effects of treatment? And I did it. How am I going to survive? Somehow, I'm doing it.” When women are faced with the fear of reoccurrence of breast or ovarian cancer, or with the occurrence of another cancer, the haunting question that I find women asking is, “I used everything that I had to fight the original cancer. How could I ever get enough strength to fight this again, and could I survive this again?” These thoughts are, on some days, quiet and on some days, they are piercing. Women sometimes are describing that they feel like they are going around in circles. They say, “I can't believe I'm back here again. Does this fear ever disappear?” In those moments, I ask women to visualize a spiral staircase. You're going around in circles, but in the example of the staircase, you're not really in the same place. I encourage women to think about that because in a spiral staircase you can look over the banister and you can actually see where you were. You can see that in fact that you have risen from the challenges and from the adversities.

This is crucial. How you coped is as important a part of your history as the cancer itself. You know that when you first thought that you wouldn't have the strength to tolerate it, you somehow managed. And it's a history that you didn't have with the original diagnosis. So to answer my original question, is the fear of recurrence of breast and ovarian cancer different than the fear of having had one cancer and developing the other? I have come to the conclusion that the answer is clearly and decisively yes and no. It differs in that having had one type of cancer and later developing a different cancer, one is unfamiliar with the language. Monitoring and detection are not alike. Surgery is different. Treatment may vary. Resources and organizations may also be different and quality of life issues differ. But do you know what? They can also be the same. Early menopause for some, fertility issues, body, self esteem concerns, impact on intimacy and sexuality, managing family, work, and other responsibilities, tolerating side effects from treatment, spiritual challenges, fear of the unknown - these are all the same. Survivors also know how to go about finding information and how to communicate with their treatment team, how to rally their support network. Most importantly, women know the second time around that they can find the strength and internal resources where once they were unsure that they would ever get through it.

I'd like to focus the remainder of my remarks on the fear of recurrence or on the occurrence of another cancer, and to provide some coping strategy in managing these fears and concerns. Survivorship does not come without its side effects. Before a woman is diagnosed, she was healthy, she was perhaps doing the right thing, and probably never thought that something like this could happen, but it did. How can she ever really feel safe again? For many women, not knowing what caused the cancer to begin with, means that they don't know for sure what to do to prevent it from recurring or from developing another cancer. Women are

taking control by changing--in addition to what we talked about tonight. They're changing their diets, their exercise routines, their stress levels, their sleep habits, all in an attempt to distinguish possible contributing factors to developing cancer again. All of these life changes are healthy choices and I strongly encourage this. But that being said, I've had women report that when they go off the regimen even so slightly that they feel burdened by guilt for wavering and they fear the repercussions. Women with strong family histories and/or who tested positive for the BRCA gene also experience heightened anxiety. Decisions about prophylactic interventions weigh heavily on their minds. It's not uncommon for women to persevere or to even second guess themselves about surgical and treatment decisions because you just don't know what the future holds. Deciding to do proactive intervention, such as prophylactic mastectomies or oophorectomies, is also not free from psychological issues and concerns. Some women are choosing to remove currently healthy parts of themselves in order to lower the risk of recurrence. The implications of these surgeries impacts a woman's body image, her self esteem, her femininity, her sexuality, her intimacy. Women become menopausal. They also have to face the loss of no longer being able to have children naturally. Even though these decisions can be heartbreaking, in many cases they are also life saving.

I get many phone calls about women saying that aches and pains quickly set off alarms generating heightened anxieties. On top of that, determining when it's appropriate to call a doctor also becomes stressful. Ironically, while undergoing treatment, it's not uncommon for a woman to report feeling safe knowing that the members of her medical team were seeing her frequently because she's under microscopic watch. Once treatment stops, she's back in uncharted territory. She's being seen for regular visits. The time between appointments is a breeding ground for fear of recurrences.

Women also become proficient in statistics. Post-treatment fears involve counting time and calculating the probability of recurrence. Reading statistics can sometimes knock the wind out of a person. Stephen Jay Gould wrote a wonderful article entitled, "The Median Isn't the Message." What he emphasizes is that when you look at a bell curve the median or the average is in the center with rare occurrences to the left and to the right. His point is that the rare occurrences do happen, and he was going to focus on being the exception. He chose to interpret the statistics in his favor and to focus on the tail end of the curve. He would not let statistics predict how long he would live.

When developing coping strategies, there is no one-size-fits-all approach to managing fear of recurrence or the fear of developing a second cancer. Bad things have happened along life's way and you've developed coping strategies. Start with what you know worked in the past. Rally your support network. Research has shown that people who are more isolated in their thoughts and feelings are more likely to experience higher levels of anxiety. Share your fears

with someone else, so that they have permission to do the same. Communicate with your treatment team. At first you may find yourself calling the doctors more frequently, and they're used to this. However, with the passage of time and by becoming familiar with your new baselines, you'll be better able to gauge when you need to consult your physician. It's important to stay educated. Thank goodness we're living in an age of information. Surf the net, continue to attend conferences, and stay in touch with organizations that have helped in the past, such as Sharsheret. The side effect of information, however, is that it can also be overwhelming. Research in cancer can be exhausting. Erma Bombeck once said that she had a theory about the human mind and that she felt that the brain was a lot like a computer, and it will only take in so many facts and then it will go into overload and blow up. Take a rest sometimes and pace yourself and realize that not all the information applies to you, obviously. If you have questions, clarify it with your treatment team. Genetic testing falls under this category, as we heard this evening, of staying informed. How you choose to proceed is in your control, but at least you can make educated decisions. Remember that you are part of a treatment team and don't hesitate to bring information or questions to the team.

It's very often that women are calling Sharsheret and they're telling me that they've requested from their medical teams to perform blood tests or scans when the doctor originally didn't suggest it. That's because the doctors really respect them as part of the treatment team and they've agreed to follow-up. It's important for you to trust yourselves and to be your own advocates. Healthy living includes making good dietary choices and exercise, regular checkups and follow-ups because fear of recurrence that makes you vigilant is good. Denial puts you at increased risk.

Remember that there is an overlap between breast and ovarian cancer and the treatment process. The waters are not as unfamiliar as they were with the original diagnosis, and it makes navigation a little bit more tolerable. As always, cry all you want, laugh all you want. There really is no limit on either. There's also a difference between what ifs and what is. There are hundreds of what ifs that are keeping women up at night. I found that women are overachievers when it comes to imagining worst case scenarios. But no matter what, it still remains an unknown. What I would like you to do is to try to focus on the what is. Fact - you have lived through what most women fear and, that is, a diagnosis of cancer. Fact - you've made it through other crises, so you come prepared. Fact - there are thousands of women with every stage of cancer living their lives fully.

How can Sharsheret be of help? As many of you know, we have the Link Program and you're involved in it. That's where we can connect you with other women who have faced similar fears and concerns regarding recurrences or the occurrence of a second cancer. And your Link can offer you tips, advice, and support. Sharsheret's booklet, "Breast Cancer Genetics and the Jewish Woman"

is designed to answer frequently asked questions about hereditary breast and ovarian cancer and its impact on the Jewish woman. I also encourage you to visit the Sharsheret website at www.sharsheret.org and download transcripts from prior symposia. I would specifically recommend on this topic, "Breast Cancer Genetics: The Impact on the Jewish Woman and Her Family," "Hormones and Breast Cancer: Through Treatment and Beyond," and "Surviving Young: Life After Breast Cancer." We also have quality of life programs, family focus, and the Sharsheret forum.

In conclusion, life is still happening and doesn't go away because of cancer. I once received a moving phone call from a woman asking for a Link because she was awaiting results of a pathology report indicating whether or not there had been a recurrence. What she said was, "I realize I can't control the cancer from infiltrating my body, nor from invading my thoughts. But what keeps me going is the realization that my *neshama*, my soul, remains cancer-free. And, this is my essence."

V. Question and Answer Session

Elana Silber: Thank you, Shera. We're now going to begin the question and answer session. If you have questions, Debra will come around and she can collect them. Given the hour, we will likely not have time to address every personal question. If the questions are of a general nature, we'll be able to get to them.

I'll start with this question. At what age should a teenage girl with a family history of breast and ovarian cancer begin considering genetic testing and other screening?

Dr. Noah Kauff: The first question is whether or not there is an identified mutation in the family. The reason for that is, again, in most cases genetic testing is more helpful if we start testing with someone who is actually affected. That's because if we can find what caused the cancer in the family, we can then have a definitive test as to whether or not someone is at increased risk compared to the general population or not.

In terms of let's say there is an identified mutation in the family, is there a role for testing a 15 or 16-year-old woman for testing? I would argue probably not. The reason which I say that, and the genetics community feels quite strongly about this, is that there are no risks of cancer to women in their pediatric or adolescent years from hereditary breast ovarian cancer syndrome. Given that there are no risks of cancer and nothing that we do differently, we feel it's important that we don't take the decision away from that young woman for when it is the appropriate time for them.

The question is whether or not there may be a role for counseling. That is something which as a genetic counseling service we do do. Our kids are all far more internet savvy than we will ever be. They will say, "Mom, you had breast cancer, Grandmother had ovarian cancer, and we're Jewish." They put those three things - breast cancer, ovarian cancer, and Jewish - into Google, and they will come up with more things than any of us would want to know. It's not going to be uncommon that these young women are going to begin to ask questions, and those are appropriate. Some of those questions, even though you may have had genetic counseling yourself, you might not be able to handle entirely on your own. That's where a genetic counseling service can help. It's appropriate because we certainly do counsel adolescent women, and frequently in the context with their family, to help put risks in perspective. The one biggest thing is you are not going to get cancer. You are not going to get cancer in the near future. We're not even sure if you'll ever get cancer. It's something which it's reasonable to talk about, but probably we - in most cases - recommend deferring of testing.

Elana Silber: There's a question that came in. I'm not sure, Dr. Poynor, if you agree with this or not. One of the audience members wants to know: Why does there seem to be such a lack of knowledge of the BRCA gene mutations among gynecologists, breast surgeons, and even medical oncologists in the community? Do you find that that is the reality or is this a specific situation that doctors are not aware of?

Dr. Elizabeth Poynor: I think that reality is actually changing. I think when I first started in my practice 11 years ago, people with ovarian cancer would come in with these huge family histories. You would clearly see a hereditary pattern to the breast and ovarian cancers and prophylactic surgery wasn't discussed. We didn't have genetic testing. The BRCA1 gene was cloned back in 1994. As the knowledge of the BRCA1 and 2 genes has gotten out there now, and the risk associated with a mutation in one of these genes has been better defined, I think that the medical community is much better educated. ACOG, the American College of Obstetricians and Gynecologists, has publications. They have active educational programs involving genetic counseling and testing and the recognition of the women who are at high risk, as well as the Internal Medicine Society. I think that there is still a cadre of physicians who may not be as on top of things, but I think that that group is getting smaller and smaller.

Elana Silber: There's a question that comes in about testing teenage boys who have a family history of breast cancer. Dr. Kauff, does it apply to boys also?

Dr. Noah Kauff: I think it also becomes entirely appropriate that there, again, is probably not a role for testing an adolescent male. There may in fact be a role for counseling for the exact same reasons which there is a role for counseling the adolescent woman. In terms of the thing which I would again emphasize is--in terms of starting the testing is, we do want to start it with the generation above. It is much more informed of us first to talk about when testing becomes appropriate for either that son or that daughter to figure out whether or not someone is actually at risk and do we have a causative mutation. I would probably defer testing an adolescent male. I think it's perfectly reasonable to have an age appropriate discussion, also with the help of genetic counselors in that situation.

Unidentified Audience Participant: I'm a pediatrician. What if after counseling, the 16 or 17-year-old says, I want to be tested because if I turn out negative, then there's a 50% chance that I'm negative and I want to know that now.

Dr. Noah Kauff: It's a difficult situation and there isn't a right answer. That's one of the reasons why all genetic counseling at any age we do in the setting of pre-test counseling. One of the things which we try and do in that pre-test counseling scenario, is to lay out why we might want to defer this. As you as a pediatrician know far better than myself, but there's a huge difference between 15 and 18.

There's a huge difference between 18 and 28. We all think we are very wise when we are adolescents. Okay, I think I'm very wise right now, but I will rapidly find that I am not a year from now. This is where as health professionals we have to help guide our patients and our parents. Can we say you can't stick out your arm? Hopefully, it doesn't get there. That's where you do the upfront counseling to prevent that decision where everyone has drawn their line in the sand.

Unidentified Audience Participant: And for a young adolescent woman who wants to be on birth control. It could potentially affect what type of birth control you might prescribe. Would you just assume that they were positive and choose--or no?

Dr. Noah Kauff: Actually, a patient asked me that question today: "Should we be testing my daughter?" Is it reasonable for her to use birth control? As Dr. Poynor mentioned, there is thought to be a decreased risk of ovarian cancer with the use of oral contraceptives and generally the combination oral contraceptives, which is the most commonly used type in this country. There is a caveat to that. That caveat is that there is actually one study out there that has suggested that use of oral contraceptives in the setting of a BRCA mutation may increase the risk of breast cancer. When you actually look at the numbers, it's something which we borrow from Peter to pay Paul. The overall cancer risk is likely about the same though different. Different cancers become more or less prevalent. Given that what I generally counsel for almost all of the patients in my practice, still the best reason to be on oral contraceptives or not is reproductive control. Where the exception is, as Dr. Poynor showed, is the data suggests that we probably get most of the benefit we're going to see from oral contraceptives from an ovarian cancer prevention standpoint after about six to 10 years of use. That will actually confer a very prolonged protection against ovarian cancer. Such that if I have a patient with a documented mutation and they've been on oral contraceptives for that six to ten years, I actually want to start thinking about perhaps getting them off because I've gotten most of the benefit I'm going to see from an ovarian cancer standpoint, but I may be paying for it with a breast cancer risk. The thing is that six to ten years gets us through the adolescent years and then gets us to the point where we can talk about testing in a much more appropriate manner.

Elana Silber: A young woman at the age of 21 had a large ovarian cyst removed and has a form of polycystic ovarian syndrome. Is she at a higher increased risk for ovarian cancer? There is a family history. The paternal grandmother passed away from breast cancer at the age of 44. Is this 21-year-old woman at a greater risk for ovarian cancer?

Dr. Elizabeth Poynor: In terms of just PCO (Polycystic Ovarian Syndrome) in general, polycystic ovarian disease is not considered a risk factor for ovarian

cancer. It's actually a risk factor for endometrial cancer because these women are anovulatory, so they see a more prolonged exposure of estrogen and don't get the monthly progesterone. Individuals in that situation are usually managed with hormonal agents, either oral contraceptives or progestational agents. In terms of elevated risk of ovarian cancer, a paternal grandmother with breast cancer at the age of 44, if she's of Ashkenazi Jewish descent, would be in that group of women that you would really begin to discuss genetic testing with. It would be very informative to know if her grandmother had tissue available or if she were still alive to have genetic testing performed. That would be based on the results of genetic testing in the grandmother. That highlights an important factor. In pedigree taking, you should always try to take three pedigrees and look at three generations of family members in considering your risk because BRCA1 and BRCA2 gene mutations are passed down through the paternal lineage, so that it becomes very important to look at those relatives also.

Elana Silber: Dr. Poynor, you mentioned that Tamoxifen was approved for women 35 and older. What are your thoughts about women under 35 taking Tamoxifen?

Dr. Elizabeth Poynor: I think that that's actually a question for a breast cancer expert. My expertise lies in ovarian cancer prevention. I work very closely with the breast medical oncologists. I actually wouldn't feel qualified to answer that question.

Elana Silber: I have a question about insurance. If someone has had breast cancer and they want to go for genetic testing, will the insurance company cover it? Would the insurance company cover treatment for a recurrence?

Dr. Noah Kauff: In terms of, will they cover the genetic testing? That one you have to speak to your insurance carrier. Of the people in this room, almost every one of us has a different insurance plan - even if we have the same company - from each other. In terms of the coverage of testing that's something which depends on whether or not there are preventive health benefits. However, in terms of the cost of counseling, for example, at Memorial, it runs several hundred dollars for the counseling. If we're testing for the three common Ashkenazi Jewish mutations, that testing runs about \$450. It's not a trivial amount, but it's something which frequently is within the realm of testing for many individuals. There are mechanisms for people who cannot afford that level of cost, even if you are paying out-of-pocket. Many insurance companies do cover it.

What is, I think, the bigger concern as we talk about insurance is the concern about insurance discrimination. That is discrimination because of a result of having had a test and people will use this against you in terms of getting health insurance, life insurance, and long term care insurance. As a genetic counseling community, we're probably the ones who initiated this fear, and now it's the

Pandora's Box we would have loved to have never opened.

The reason which I say that is at Memorial we have tested over 4,000 individuals in the last 10 years. Nationally, there have been over 80,000 individuals tested. There is not a single well documented case of discrimination in health insurance or employment as a result of testing for BRCA1 or BRCA2 mutations in this country. There are some isolated case reports of individuals who have had discrimination in terms of life insurance and long term care insurance.

The question is, however, even if you've never had cancer, if your mother had breast cancer at 45, your aunt had ovarian cancer, your grandmother had breast cancer, and we throw in the fact that you're of Eastern European Jewish heritage. If I'm an insurance company actuary, I don't need a genetic test to say I've got to be concerned here. The reason we spent so much time as a genetic counseling community a decade ago talking about this is we weren't sure we could do anything to alter the natural history. If we couldn't change the risks of women who had these predispositions and we were just making them uninsurable, it did not make a lot of sense. We spent a lot of time talking about discrimination. We haven't seen it. Can I promise it won't ever happen? No. But what I do know is in the last 10 years, we've actually learned we can alter the natural history. Now we have this theoretical risk versus this - in my mind - a very real benefit of testing. I think we have to put it in perspective. We can't promise that you'll never see discrimination. It's not been a big issue. But I think now we can really act on the information. So I think we've tried to, as I said, close that Pandora's Box somewhat.

Unidentified Audience Participant: If a person has the testing done, pays out-of-pocket, does it have to go through the records? This way you're not dealing with insurance, if a person just wants to do it for their own self.

Dr. Noah Kauff: Here's my thought process on that. There was a time where a lot of that occurred. However, if you are unaffected, if you find out you're positive, you or your daughter or your relative who is 30 years old is unaffected, and all of a sudden is now saying, I'm going to be getting breast MRIs, the test is the inexpensive part - a breast MRI, a bilateral breast MRI - on the order of \$1,500 to \$2,000 a year. Those are things which are appropriate in the setting of a genetic testing. There are now published national recommendations that they should be included as part of this screening. It's something which your actions, since we now are acting on the information, will actually tell the result. Additionally, it's very difficult for your providers to follow you. Because, as I mentioned, BRCA1 and BRCA2 are related but not identical cancer susceptibility syndromes. There is difference in the timing of the risks. We're beginning to use that to manage your care. Unless we can put it in your records, we can't--I can't remember when I see you six months or a year from now what I'm supposed to be doing.

VI. Symposium Conclusion

Elana Silber: As we wrap up this evening, please join me in thanking our speakers for generously sharing their time and expertise with us. I would also like to thank our sponsor once again for bringing us all together - the North Jersey Affiliate of the Susan G. Komen Breast Cancer Foundation. I would like to thank Steve Fox from Fox Marketing, who helped with all of the audio/visual tonight.

I'd like to make a special note that in each one of your packets there's a yellow evaluation form. Whether you're a patient or a healthcare professional, I would encourage you to fill out the evaluation form. The feedback is very important to us to help us with future programs and to better serve the women of Sharsheret.

Thank you all, again, for joining us this evening to explore the connection between breast cancer and ovarian cancer. A transcript of the event will appear on Sharsheret's website, www.sharsheret.org, in a couple of weeks. We look forward to continuing this important conversation about breast cancer and ovarian cancer, and hope to share new research in the years to come.

Good night.

VII. Speakers' Bios

Shera Dubitsky, M.Ed., M.A. is Sharsheret's Link Program Coordinator. Ms. Dubitsky served as a Psychology Resident and Fellow at the Bronx Psychiatric Center of the Albert Einstein School of Medicine, and an Associate Psychologist for the Jewish Board of Family and Children's Services. She has also worked as a Researcher at Memorial Sloan-Kettering Cancer Center. As Sharsheret's Link Program Coordinator, Ms. Dubitsky assists women newly diagnosed and at high risk of developing breast cancer, and provides supportive counseling to women living with metastatic breast cancer. She also assists in the advancement and development of programs addressing the needs of the women of Sharsheret.

Noah D. Kauff, M.D. is a gynecologist and geneticist who specializes in the care of patients who may have an inherited predisposition to cancer. He evaluates and treats all hereditary cancer syndromes, including those that cause an increased risk of breast, ovarian, colon, uterine, thyroid, and other cancers. His clinical areas of expertise include cancer risk counseling, screening for and prevention of inherited cancers, and providing gynecologic care to cancer patients. Dr. Kauff's research interests include: The effect of genetic counseling on the evaluation and treatment of women with an inherited predisposition to cancer; the effect of risk-reducing surgery for the prevention of breast and ovarian cancer in women with inherited predisposition to these cancers; and the identification of genetic and environmental markers that may allow risk-reduction strategies to be tailored to individual patients at increased risk for cancer.

Elizabeth Poynor, M.D., Ph.D., FACOG is a gynecologic oncologist and pelvic surgeon who focuses on the comprehensive surgical management of gynecologic cancers and works with medical and radiation oncologists to facilitate a compassionate, multidisciplinary approach to the management of women's cancers. She has special expertise in the complex management of women and their families who have a genetic predisposition to developing breast cancer and gynecologic malignancies. As a surgeon scientist, Dr. Poynor's work focused on translating basic science principles into clinically meaningful treatments and she served as Director of Translational Research for the Gynecology Service at Memorial Sloan-Kettering Cancer Center. She has also served as an investigator in numerous clinical trials relating to surgical, medical, and biological treatment of gynecologic cancers.

VIII. About Sharsheret

Sharsheret is a national not-for-profit organization linking young Jewish women in their fight against breast cancer. Sharsheret (Hebrew for chain) pairs young women facing breast cancer with volunteers who can share their experiences, both personal and medical.

Sharsheret's programs respond to the needs of the women we serve and include:

- **The Link Program**, a peer support network connecting young women newly diagnosed or at high risk of developing breast cancer with others who share similar diagnoses and experiences.
- **Education and Outreach Programs**, including health care symposia addressing the concerns of young women facing breast cancer. Recent events addressed the subjects of breast cancer and fertility, parenting through breast cancer, breast cancer genetics, and surviving breast cancer. Transcripts of all symposia are available on Sharsheret's website, www.sharsheret.org.
- **Quality of Life Programs**, including the Busy Box for young parents facing breast cancer, Best Face Forward to address the cosmetic side effects of treatment, and Embrace, a support program for young women living with advanced breast cancer.

For more information about participating in Sharsheret's programs, please call toll-free (866) 474-2774. All phone calls are confidential.

Sharsheret is grateful for the generous support of:

The North Jersey Affiliate of the
Susan G. Komen Breast Cancer Foundation

IX. Disclaimer

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