

Breast Cancer Genetics And The Sephardic Jewish Woman

Symposium Transcript
Sephardic Community Center
Brooklyn, New York
Wednesday, March 26, 2008

Presented By:



Linking Young Jewish Women in Their Fight Against Breast Cancer

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I. Introduction

Elana Silber: Thank you, everyone, for joining us at our symposium, *Breast Cancer Genetics and the Sephardic Jewish Woman*. I am Elana Silber, Director of Operations at Sharsheret, which is Hebrew for "chain," and we're a national organization supporting young Jewish women facing breast cancer. I will soon have the pleasure of introducing our distinguished speakers, who will share their insights into what has become an urgent topic for the women of Sharsheret, breast cancer genetics.

I would like to begin by thanking those who have made this important event possible. A generous grant from the Greater New York City Affiliate of Susan G. Komen for the Cure enabled us to prepare the information packets you have each received, as well as the professional taping of this event. We're fortunate enough to have Cara Thunder from Susan G. Komen for the Cure, and we really appreciate the support that we've received from Komen the last few years and for all the different events that we've partnered with. We will be taping a DVD of this event to make it available to those who cannot join us this evening. We would also like to thank the Sephardic Community Center for opening their doors for this important event, and in particular, we'd like to recognize, once again, Sari Setton and Linda Eber, who took a lot of time and effort to spread the word and make this evening what it is and for the ability to share with the community this information that may not have been accessible to them without this. And, we want to thank MedStar and the Sephardic Bikur Holim for sponsoring this symposium. Sharsheret's staff and volunteers have worked tirelessly, and we'd like to recognize Ellen Kleinhaus, who's here with us tonight. She's the Senior Program Coordinator who organized this event.

Some of you with us tonight may be healthy but want to know more about taking care of yourself. Others here tonight are also healthy, but perhaps facing the risk of breast cancer. Maybe there's significant family history of cancer and you have these questions: What does proper breast care mean? What do I need to know about breast cancer genetics and its impact on me, a Jewish woman of Sephardi descent? What are the risks and downsides of genetic counseling, genetic testing? What impact will the information I learn tonight have on the other members of my family, my mother, my sisters, my daughters, and my friends around me? And, where can I turn to for support, resources, and information?

Our speakers tonight have volunteered their time to address these important questions and more. They have also agreed to shed light on an area of breast cancer genetics that had received little prior attention, the impact of hereditary breast cancer on Jewish women of Sephardi descent. We will also hear from Sharsheret's Executive Director, Eillene Leistner, about the needs of Jewish families at risk of breast cancer and how the Jewish community is pulling together under the guidance of Sharsheret to share information, resources, and support with those of us who may need it the most. And, finally, all of the speakers tonight will be happy to take questions from our audience.

Our goal tonight, and with this DVD, is to answer some of the critical questions that have been brought to our attention, raise new ones, and generate discussion about the ways in which breast cancer impacts the Sephardic Jewish woman as an individual, as a family member, and part of a broader community. This is the beginning of what is certain to be an ongoing conversation in your community, and we encourage you to stay involved as the Sharsheret, the chain, continues to grow in the years ahead. During the presentation this evening, please feel free to jot down any questions you may have. There are index cards in each information packet. Once the presentations are complete, Ellen and I will go around the room collecting the index cards, and we'll raise the questions to the panelists. In the interest of time, please keep your questions general in nature.

It is now my pleasure to introduce Dr. Ruth Oratz.

For years, breast cancer research has focused primarily on the Ashkenazi Jewish woman, with almost nothing written about women of Sephardi descent. Dr. Oratz is an Associate Professor of Clinical Medicine at the New York University School of Medicine and Founder and Director of the Women's Oncology and Wellness Practice in New York City. Dr. Ostrer is Professor of Pediatrics, Pathology, and Medicine and Director of the Human Genetics program in the Department of Pediatrics at New York University School of Medicine. Tonight, they will review the guidelines for maintaining breast health and recommended breast cancer screening methods and share with us the emerging research of Sephardi Jews and the genetic susceptibility to breast cancer. Please join me in welcoming Dr. Ruth Oratz and Dr. Harry Ostrer.

II. Presentation by Ruth Oratz, M.D.

Dr. Ruth Oratz: Thank you, Elana.

Tonight, we're going to be focusing on a number of different questions that relate to breast cancer and specifically to the genetic susceptibility to breast cancer. I'm going to start off by giving you some general information about breast cancer statistics and then some general information about the clinical presentation of breast cancer. From there, we'll go into discussing the genetic aspects.

Breast cancer is the most common malignancy in women, and this year in the United States, about 200,000 women will be diagnosed with breast cancer and about 40 or 50,000 will die from breast cancer this year in the U.S. That means more than 150 women are dying every day from breast cancer. About 5 to 10% of women who are diagnosed with breast cancer have a significant family history and a genetic predisposition to developing breast cancer.

Let's start at the beginning of the clinical story. How is breast cancer diagnosed? Most often, there are two ways that we diagnose breast cancer. Either a woman feels a lump in her breast on self-examination, or her doctor feels a lump when she goes for a physical examination, and that we call a palpable mass in the breast. Or, on breast imaging. The most common form of surveillance, of screening, for breast cancer is mammography, and our current recommendations are that all women over the age of 50 have an annual screening mammogram, and for women over the age of 40 who have no special risk for breast cancer, a mammogram every one to two years. I think in the New York area, most of us are recommending annual mammography, however, for women over the age of 40. There are other techniques that we can use to image the breast -- ultrasound or sonogram and now also MRI. We don't have screening guidelines for the general population for ultrasound or MRI. The general population screening guideline is for mammography.

Mammography is the oldest modality. We've been using it since the 1960s and 1970s for screening breast cancer, but we have learned that ultrasound and MRI are very, very helpful in looking at the breast tissue with another technique. Especially in young women under the age of 50, breast tissue may still be very dense because of hormonal factors that are operating, and mammograms may not show us everything we need to see. About 10 to 15% of the time, there may be a cancer in the breast that is not detected by mammography. Ultrasound and MRI are other imaging techniques that can be very helpful to us. In women who are at very high risk for breast cancer -- we'll talk about that a little bit later on this evening when we delve into the genetic susceptibility to breast cancer -- we are increasingly using both ultrasound and MRI in addition to mammograms for screening for breast cancer. If a woman is diagnosed with a breast cancer, either because of a lump that she felt in her breast or because it was seen on a mammogram, very often, we will use the ultrasound or MRI to help us confirm that diagnosis, to find that spot and allow us to do a biopsy of that specific location, and we

also use those other imaging techniques to make sure that there's nothing else going on, that there aren't any other spots that are of concern. Breast surveillance with physical examination, self-examination, and mammography is the starting point, and then we layer on top of that ultrasound and MRI when it's needed.

If we see a suspicious lesion either on the mammogram or because someone felt a lump, then we proceed with a biopsy, and there are many different ways these biopsies can be done with various types of needles, but the biopsy gives us the diagnosis of cancer.

Once a woman is diagnosed with breast cancer, she then goes on to a long series of tests and steps along the way until she actually gets to treatment. But one thing that's very, very important to understand is that breast cancer is not just one disease. It really is a spectrum of different clinical presentations. I'm not going to go into the detailed biology of breast cancer, but there are subtle differences in the types of breast cancer that women develop that may lead to different recommendations about treatment with surgery, with radiation therapy, with chemotherapy, hormonal therapy, or even biologic treatments.

When a woman is diagnosed with breast cancer, one of the questions that we, the doctors, ask and that you're going to ask of us is how far along is this cancer, how advanced is it, and we refer to that as the stage of the cancer at presentation. Staging of breast cancer is really a very old system and is based on information that we had available to us 30, 40 years ago. How big is the primary tumor? That's what the T stands for. Is there involvement of the lymph nodes? And that means predominantly the lymph nodes under the arm or in the axilla. That's N. And M, which means has there been spread beyond the breast and the lymph nodes, or metastasis. By measuring the size of the tumor, looking at the lymph node involvement and determining whether or not the cancer has spread, we can assign a stage. Treatment is largely based on how extensive the cancer is at the time of diagnosis, that is the stage, but also on the biologic characteristics of the tumor.

On the next slide, you'll see some of the risk factors that are important for the development of breast cancer. Anything that affects your chance of getting a disease is a risk factor. What are examples of risk factors? You know that smoking is linked to lung cancer. Too much sun exposure may lead to skin cancers. What are the relationships between these risk factors and actually getting the disease? And there are different kinds of risk factors. Some of them you can change, and some of them you can't. You can make a decision about whether or not you want to smoke, but you can't change the fact that you're a 62-year-old woman. You can't change that. There are risk factors that are environmental and behavioral, those we might be able to alter, and there are some factors that we can't change, and among these are our family histories and our genetic risk of developing cancer.

With respect to breast cancer in specific, we know that there are risk factors that

increase a woman's probability of developing breast cancer. If you've already had one breast cancer, the risk of developing a second breast cancer is a little bit higher than if you never had breast cancer in the first place. The older we get, the higher the incidence is of breast cancer. The average age of diagnosis in the United States is 60, but that's not to say that we don't see patients even as young as in their late 20s and all the way through lifespan into the 80s and 90s. With each decade of life, the risk actually increases.

We know that factors related to reproductive cycle and reproductive life are important in trying to ascertain the risk of breast cancer, and that is the age of menarche or the first menstrual period, the age of menopause, the timing of the first pregnancy, and how many pregnancies a woman has had. All of these factors seem to relate to the environment within the body that's controlled by the hormones estrogen and progesterone. We know that there may be a link to using hormone replacement therapy after menopause slightly increases the risk of breast cancer. The data about whether or not birth control pills increase or decrease the risk of breast cancer is somewhat controversial, and it's really not clear that there's any definite association.

If a woman has had a biopsy of an abnormality in the breast because something looked suspicious on a mammogram or because she felt a lump, even if that didn't show cancer but if it shows cells that are atypical or perhaps precancerous, that might lead to an increased risk of ultimately developing invasive breast cancer.

And then there are a few other risk factors that are less common but should just be mentioned. Young women who have been treated for other types of malignancies, particularly Hodgkin's disease or lymphoma, and who have received radiation therapy to the chest area, we know are at increased risk for later on, 10 or 20 years later, developing breast cancer, and those young women should be watched very closely.

We also know that some of our behaviors are linked to breast cancer, that in older women, in post-menopausal women who are obese, and I mean really obese, not five or ten pounds overweight, that there is an increased risk of breast cancer, and we know that for women who exercise regularly at every age, there seems to be a slight decrease in the risk of breast cancer. That's just good for your general health anyway; stay active and watch your diets. There is a link to alcohol, but it's really for women who drink a lot. More than two drinks every single day leads to a somewhat increased risk of breast cancer, but moderate alcohol intake is not really a problem.

Now let's come to really what is the germ of what we want to discuss this evening, and that's family history and genetic susceptibility to breast cancer. And as I mentioned earlier on, about 10% of women who develop breast cancer will have a family history. What does that mean, family history? Well, what we're looking for are relatives who are close to that patient who may have had breast cancer themselves, first-degree relatives. That means a parent, a sibling, or a child, or even second-degree relatives -- grandparents, aunts and uncles, cousins, and so on, grandchildren.

In women who develop breast cancer, many of them, 20 or 30% of them, will have a family history, but only 5 or 10% will actually have at least a known genetic cause for this. When we look at families, we want to ascertain how many other relatives have had breast cancer and how close they are in their relationship to the individual who's just been diagnosed. And the other very important factor in the family history is if there ever has been any male anywhere in the family with breast cancer. That is really a red flag to us that there may be a genetic factor. The family histories that are high-risk to us are those where there are many individuals in several generations who have been affected with breast and/or ovarian cancer because there is a link to ovarian cancer; early-age onset, young women with breast cancer; or male breast cancer.

What does this mean if there's a family history and if we think there's a genetic susceptibility? What are these genes doing that are causing cancer to develop? All cancer arises because a normal cell is transformed into a malignant cell, and that transformation happens because the genes inside that normal cell somehow are damaged. Because those genes become abnormal, the way they control the behavior and the growth, the proliferation, the differentiation, that means the cell behavior, becomes abnormal. A cell that was originally doing its normal job now is all off kilter and is behaving in a way that's very bizarre so that we call it malignant. That causes it to turn into a cancer cell.

It's not just one genetic abnormality that leads to the development of cancer, but several what we call "hits" have to take place in the DNA inside that normal cell. We know that in families, and in women, who are at high risk for developing breast cancer, one of the most important factors is whether or not that woman has inherited from either one of her parents an abnormality in one of the two important genes that really controls the behavior of normal breast cells, and those are called BRCA1 and BRCA2. We'll be spending a lot of time on that later on. But you can inherit a mutation. Those heritable mutations provide that first "hit," the susceptibility, the underpinning that if additional damage occurs to that cell, it will ultimately lead to the development of a cancer.

And some of those risk factors we mentioned before. They may be exposure to radiation. They may be environmental factors like smoking and diet, exercise, and even factors that are yet unknown to us.

What evidence do we have that there could be a hereditary predisposition to cancer? Well, we know that when we take family histories from women who have had breast cancer, as I mentioned, 20 to 30% of them will tell us that someone in their family had breast cancer. If we look at twins, we can see that if they are identical twins, there is a higher rate of cancer in those twins, suggesting twins share exactly the same DNA, identical twins. If we look at those studies of identical twins, those are the monozygotic twins, there's a higher rate of developing cancer, and those are the numbers under the MZ column, compared to the fraternal twins, or dizygotic twins. That suggests to us that those twins with the identical DNA have inherited something that they share.

Again, to summarize, the factors that are suggestive of hereditary cancer, and particularly hereditary breast cancer, are more than one individual affected in the same family, frequently in multiple generations; early-age onset, and for breast cancer, early-age onset in most studies is considered less than age 50, certainly less than age 40; if an individual has multiple primary tumors -- a woman who has cancer in one breast and then develops a cancer in the opposite breast or a woman who has breast cancer and then develops ovarian cancer; or if we see cancers that we know are linked together -- breast, ovarian, prostate, pancreatic cancer -- all in the same family, lots of people with multiple cancers in the same family, that's worrisome to us; and, again, male breast cancer.

Just looking at some of the different types of cancers, this is a general overview of breast cancer, ovarian cancer, colorectal cancer, and prostate cancer, and across the board, you can see that we think about 5 to 10% of all of these cases of cancer may be linked to an inherited predisposition that confers a high risk of developing these cancers. These estimates, based on family history, were developed before we actually knew which genes were involved, but we could look at the family histories and say, okay, how many relatives under the age of 50, who were close relatives, first-degree relatives, had cancer, and then we could predict the risk that another -- that that individual would develop cancer. Likewise, we can tabulate these risks based on the age and the number of relatives and their closeness on the family tree.

The genes that are related to the increased risk of breast cancer are the BRCA1 and BRCA2 genes. These account for about 90% of the inherited susceptibility to breast cancer. But there are other genes that we know of that also are linked to the increased risk of breast cancer -- ATM gene, [check 2], P53 and P10 -- and these are syndromes that are much less common. These genetic mutations are found less frequently, but we do identify them, and in certain families, we certainly do screen for them.

If someone has inherited a mutation in one of these several genes, what is actually the risk of her developing breast cancer? For mutations in the BRCA1 gene, the risk of developing breast cancer by age 70 is in the range of somewhere between about 50 and 85%. That's a very high risk, very high risk. If someone has inherited a mutation in the BRCA2 gene, the risk may be a little bit less, maybe in some studies as low as 35 to 40%, but other studies show that in families with BRCA2 mutations, that there may be as high a risk as 85%. Mutations in P53 are associated with several different types of cancer -- brain cancer, uterine cancer, ovarian, breast cancer. The P10 mutation is associated, as well, with thyroid and breast and uterine cancer. And then we can see the MSH mutations are linked to colorectal cancer and other GI tract cancers.

Let's focus on the two genes that we know are most commonly linked with inherited susceptibility to breast cancer, and that's BRCA1 and BRCA2. Genes live on chromosomes, and we number the chromosomes, and every chromosome has a matched pair. We have two chromosomes for each number. BRCA1 lives on

chromosome number 17, and BRCA2 lives on chromosome number 13. And mutations in either one of these genes are the most common ones that are associated with breast or ovarian cancer. We think that the function of these genes normally, when they're completely normal, no mutations, is to help prevent cancers from developing. When the gene becomes abnormal, when it has a mutation in it, it no longer performs its normal function, which is to suppress the development of cancer, and that then allows a cancer to develop. It allows that second, third, and fourth and fifth hit to take place and for the cancer to actually develop.

And this is a slide that shows the normal DNA. When there's damage in it, the body tries to repair it, but if there's a mutation in one of these genes, BRCA1 or BRCA2, and there's failure to repair the mistake that happens in the DNA as these cells are multiplying over time, that can lead to another hit, perhaps a P53 mutation, and ultimately lead to the development of cancer. As we're progressing with our research in this area, we're beginning to understand more and more about the pathways that lead to the acquisition of these mutations over time.

Does every single person who has inherited an abnormal BRCA gene develop cancer? No. If the risk is 50 to 85%, that means 15 to 50% of people who inherit this gene never get cancer. Why is that? Why is it when we look at some families, it appears that we skip a generation?

I'm taking care of a young woman in my own practice who was diagnosed with breast cancer when she was 34 years old. She does have a mutation in BRCA1. Neither one of her parents ever developed cancer. Both of her parents were tested, and we learned that her mother was the carrier of this mutated gene. Her mother is almost 70 years old and has never developed any cancer at all. Why does that happen? This is all part of our research program, and Dr. Ostrer is going to discuss with you a little bit later on how we're trying to address some of these important questions about understanding how these mutations in the BRCA genes penetrate into individuals and into families and how they express themselves.

One thing that's important to remember is that if an individual does have a mutation in BRCA1 or BRCA2, that there's a 50/50 chance that each child could inherit this mutation, whether they're male or female. We look at family trees, and I know that there's been a big interest recently in all of us going back into our own genealogies and tracing back our families to try and create these family trees. We do the same thing in medicine, and we call that a pedigree, where the genetic counselor or the physician who you're meeting with to get this family history and try to determine whether or not there's an increased risk of genetic susceptibility to cancer. The circles stand for females and the squares stand for males. We map out who all the individuals are in the family and how they're connected, either by marriage, parents, children, siblings, and so on. Then we can fill in all these little spots and dots to see who in the family was affected with cancer and does it look like there's a pattern of inheritance that suggests to us that there may be a gene that's inheritable that's responsible for increased susceptibility to cancer.

And here's an example of a family where there were multiple cases of breast and ovarian cancer. You can see that there are two women, on the right, who developed ovarian cancer, one as young as age 36. Those two women were sisters. And they had a brother, the square, that's a male, who developed breast cancer at age 63. So this is an example of a family history that's highly suspicious to us of a genetic mutation in BRCA1 or 2.

Just to summarize again, the hereditary breast and ovarian cancer syndrome linked to BRCA1 and 2, multiple family members with breast and/or ovarian cancer, family history, family history of male breast cancer, and then we see this increased risk of multiple cancers -- bilateral cancer, or more than one cancer in the same individual.

If we look specifically at BRCA1 and BRCA2 mutations and we ask the risk of developing cancer over a lifetime, there are some differences. BRCA1 seems to have perhaps a slightly higher risk of breast cancer and ovarian cancer, and the BRCA2 is linked to a higher risk of male breast cancer. When we look at other malignancies -- pancreatic cancer, prostate cancer and perhaps melanoma -- may have an increased association to BRCA2, as opposed to BRCA1.

If a woman or a man belongs to one of these families where we're suspicious and concerned about the possibility of an abnormal gene, what do we do? How do we find out about it?

The first step is to meet with a genetic counselor. A genetic counselor is a trained professional who really understands how to get a complete family history, and then based on that information, how to weigh and calculate the probability that the individual that they're speaking to might have a genetic mutation. It's important that the correct diagnosis is made if someone is diagnosed with cancer and then to determine which, if any, type of genetic testing would be appropriate. We feel that it's very, very, very, very -- did I say that enough times? -- very important that if there's a consideration of genetic testing, that the first step is genetic counseling so that you really understand the probability that you may or may not have an inherited susceptibility to cancer and then to understand the implications of what to do with that information.

The first step that we would do is to test an individual who already has developed cancer because if there's a mutation in that family and someone has developed cancer, our most likely chance of finding the mutation is in the person who developed the cancer. That's the proband. If that individual has a genetic mutation, then we could go on and test other members of the family. But, we do not recommend at this point in time, random screening or random testing unless someone either has developed a cancer herself or is in a family that fits those criteria that I already mentioned to you.

Who should consider genetic counseling and genetic testing? Individuals who have developed breast cancer, particularly at an early age of onset, individuals with a family

history of breast and ovarian cancer, or if a woman has developed both of those cancers herself. If you're unaffected by cancer, should you consider testing? Yes, if there's definitely someone in your family, a close relative, who's been known to have a mutation, or if you're in a family where there's a high susceptibility.

What's involved in genetic testing after you've met with the genetic counselor and understand the risks and benefit of testing? It's a simple blood test, one tube of blood, and we send that off to the laboratory.

Dr. Ostrer is going to speak with you in detail about the specific mutations that we look at in Ashkenazi Jewish populations and also how that may affect what we look for in Sephardic populations, and I will leave that conversation to Dr. Ostrer.

How do we use this information? What if we find out that you, in fact, do have a genetic mutation in BRCA1 or BRCA2? Well, one thing certainly is to increase the level of surveillance, to watch more carefully. We can screen for breast cancer, as I mentioned before, with self-examination, physician examination, and mammography, and we would consider adding ultrasound and MRI for a closer look, and particularly in looking at young women. If there's a risk of colon cancer, we would recommend colonoscopy perhaps at a more frequent time interval than normal. We don't have great screening for ovarian cancer, and that's very problematic for us. But there are some modalities that could be useful, including ultrasound and a blood test called the CA-125 test, but these are imperfect screening tests, and we are continuing to do more research to help us with early detection for ovarian cancer. Prostate cancer in men is often detected by examination by a physician, and of course, you've probably all heard of the blood test called PSA, which we do recommend for screening for all men over age 50 and men at high risk maybe at an earlier age. Ultrasound can also sometimes be useful.

As I mentioned, for breast cancer surveillance, we have many modalities -- mammography, ultrasound, and MRI. We also have modalities available to us to reduce the risk of developing cancer. Surveillance and screening don't prevent the cancer; they just help us find it, hopefully detect it early if it's going to develop. But if someone learns that she's a carrier of a genetic mutation, which may confer as high a risk as an 80 or 85% lifetime risk of developing breast cancer or a 20 to 40% risk of developing ovarian cancer, is there anything that she can do to reduce that risk? And the answer is yes.

In terms of breast cancer, one option that we have is to manipulate the hormonal milieu in that woman's body. Remember, I mentioned to you early on, that we think estrogen exposure of the breast tissue over a woman's lifetime is associated with the risk of breast cancer. We can use a medicine called tamoxifen, which interferes with the estrogen receptor on those breast cells, and that may help reduce the risk of breast cancer. We can also think about prophylactic mastectomy, which is a very big step, especially for young women, but has a major, major impact in reducing the risk of breast cancer. It may bring someone from an 80 or 85% lifetime risk down to less than a 5%

lifetime risk. Today with our techniques in plastic surgery for reconstruction, we can actually achieve very, very good results for women who decide to take the path of prophylactic mastectomy.

Focusing on the BRCA1 and 2 mutations, we turn to ovarian cancer and, really, in that situation, our best option for reducing risk is surgical removal of the ovaries. As I mentioned, ovarian cancer screening and prevention is trailing a little bit behind breast cancer screening and prevention, and we are concerned about this and often recommend, especially if a woman is close to menopause, that she undergo prophylactic removal of the ovaries if she's at high risk for ovarian cancer.

I mentioned that if someone has a mutation in BRCA1 or 2, they're at increased risk for developing a second malignancy and that the benefit of risk-reducing surgery is quite significant. If we look at the risk of breast cancer and we say, "What can we do to reduce that risk?" In premenopausal women, young women, who have their ovaries removed surgically, (we're reducing the amount of estrogen in their bodies), we can achieve about a 40% reduction in breast cancer occurrence. And, of course, their risk of ovarian cancer goes down dramatically, and that's another option for young women in terms of breast cancer prevention.

There's a great deal of concern about genetic counseling and genetic testing because individuals are worried that they may be discriminated against. There are regulations and laws on the books in New York State. There's the Americans with Disabilities Act, and a number of other safeguards that are in place to protect against genetic discrimination. Are they perfect? No. Has there ever been a case brought to court because of someone who was discriminated against in the workplace or in buying insurance or in anything because of carrying a mutation in BRCA1 or 2? No. The fact that there has not yet been a court case means that no one has yet been put in a situation where they felt they had to bring that case to suit. That doesn't mean that this is flawless, but we certainly encourage individuals to go ahead with testing and to speak with their physicians about what their follow-up and their surveillance programs might be and what options they may have for risk reduction and to, with caution, not let this be a barrier. And the more that we -- and not just in cancer, but in medicine in general, we understand about the genetic risk factors for many diseases, not just breast and ovarian cancer, the more we will see genetic testing as an important part of our medical therapy, and I think that we will see greater and greater protection for individual rights in this regard. I would argue always that knowledge is power and that if you feel that you may be at risk for this or you have concerns with this, to speak with your physician, if it's appropriate to have a referral to a trained genetic counselor or medical geneticist to really review your family history and the possibility that you may have an inherited susceptibility to cancer, and then to take that information and develop a plan that's appropriate for you and your family.

Before Dr. Ostrer speaks, I'm going to introduce his comments, which are going to focus on what we understand about these mutations in Jewish populations, Ashkenazi and

Sephardic, based on a story that Harry has heard me tell.

I grew up in New York and went to Einstein Medical School and then came to NYU and have been practicing there forever. But several years ago, my husband started a business in Colorado, and the next thing I knew, I was on a leave of absence living in Boulder, Colorado. The Flatirons are very pretty.

But when I got out there, I met a woman named Lisa Mullineaux, and Lisa was the genetic counselor in the practice that I joined in Denver when I went to work out in Colorado. And I came into the office one day, and she said, "You know, we have this interesting observation." Lisa and her colleagues identified in a group of women who were living in Southern Colorado, who were Spanish. They came generations and generations and generations ago from Mexico up into Colorado, and they had in their families the pattern of inherited susceptibility to breast cancer. They were very young when they developed breast cancer, and they had multiple family members with breast cancer. And they tested these women and found the same genetic mutation that had been previously thought to be associated with Jewish populations and specifically with Ashkenazi Jewish populations.

And Lisa told me that story, and I said to her, "Oh, well, they're Jews." She thought I was a little crazy. I said, "They're Jews." And then when we sort of went back through this story, it turns out that these women who were living in the San Luis Valley came from families that had left Spain, went to Mexico -- they were escaping from the Inquisition -- and then traveled up into New Mexico and into Colorado. They arrived there as early as 1598, and they just kind of stayed in this valley and lived there for the next 500 years, stuck between two mountain ranges in this valley just living there all the time.

It turned out that there were, in this study that was done, 19 patients with breast and ovarian cancer, they all identified themselves as Hispanic, of Spanish origin, and they all came from families that met our criteria for having a genetic predisposition for breast cancer, and then we tested them. Out of those 19 patients, 10 of them tested positive for a mutation in BRCA1 or BRCA2, and six of them had the specific mutation that we thought was associated with Ashkenazi Jews.

Dr. Ostrer is going to spend, I think, some more time talking about the specific mutations with you, where else we've seen them, whether or not we've seen them in Sephardic populations, and where we're going to get more information to understand how these genes not only travel in families but have migrated in populations and across the globe through history. Harry?

III. Presentation by Harry Ostrer, M.D.

Dr. Harry Ostrer: Now that Dr. Oratz has done the hard part -- she did the part that she usually does and that I usually do, so I get to do the fun part, which is to talk a bit about BRCA1 and 2 mutations in the context of Jewish history and also some of the contemporary studies that we're doing right now.

In fact, I've been interested in the genetics of Jewish populations for quite a long time, in fact, since I was a medical student at Columbia, and I organized a screening program for Tay Sachs disease for the Jews living in Riverdale. Actually, it turns out now that Tay Sachs disease was not just an Ashkenazi Jewish disease, as we typically think about it, but it's also a Sephardic Jewish disease occurring among Moroccan Jews and also Iraqi Jews.

And it's kind of interesting because in each of those population groups, there are specific mutations for Tay Sachs disease, but as you've heard from Dr. Oratz, in fact, there were shared mutations that occur among Ashkenazi Jews and Sephardic Jews. And we would date two of these three mutations, the 185 del AG mutation in BRCA1 and the 6174 del T mutation to the Palestinian times to the Kingdom times of Jews in Palestine. And, in fact, it would explain why we see the 6174 del T BRCA2 mutation and the 185 del AG mutation in BRCA1 in several different Jewish populations. In fact, when we put these together, we've observed them in Tunisian Jews, Ethiopian Jews, Iraqi Jews, Moroccan Jews, and Syrian Jews. It's the same mutation. Some of you may say, well, gee, the mutation may have occurred twice in different parts of the world, but in fact, that really isn't the case.

We can look at the so-called genetic background on which these mutations occurred, and we found that, well, lo and behold, it's exactly the same for the 6174 del T mutation and the 185 del AG mutation. And this terminology refers to the fact that, actually, deletion of one of the base pairs or two of the base pairs of DNA is occurring, disrupting the function of these genes.

In the context of looking at Jewish history, in fact, we can see that mutations have occurred throughout our history, and, in fact, we can use the occurrence of these mutations to sort of date key events. There are, as shown in the upper left-hand side there, mutations for deafness, for familial Mediterranean fever, the blood disorder, G6PD deficiency, and cystic fibrosis within the Kingdom times of Jews, not only BRCA1 and 2 but also mutations for Factor XI, a clotting disorder, combined factors V and VIII deficiency, also a clotting disorder, LRRK2, a gene which, when mutated, increases risk substantially for Parkinson disease.

The Hexosaminidase A mutation that occurs in Iraqi Jews probably dates from the time of the Babylonian conquest and exile, and as many people have heard, there is a -- it's not really a set of mutations, but it's a set of variants on the human Y chromosome that serve as a marker for shared ancestry among male Cohanim.

And I've thrown in some bits of art, if you will, and also, although you don't necessarily appreciate it there, that triangular shape is the House of David inscription that tells us, in fact, that there was a King David. The House of David inscription is now located in the Israel museum, but the inscription, unfortunately, describes the defeat of one of David's descendants at the hands of the Syrians.

Let's move on. As you've heard, not only has the common 185 del AG mutation been found in Jewish populations, but it's also been observed in U.S. Latinos. The clue to this, as you've heard, was the study originally conducted in the San Luis Valley in Colorado, but, in fact, there was a BRCA1 and 2 genetic epidemiology study that was conducted in the Bay area cohort of people with cancer, which included people of many different ancestries. And what mutation should be most common among the Hispanics in the Bay area? Lo and behold, it was 185 del AG. In fact, this shared Sephardic ancestry is coming to the New World and then intermarrying with other Spaniards or other people, losing their ethnic identity as Jews. In fact, it's not confined to Northern New Mexico and Southern Colorado, but in fact, it's pretty common among the U.S. population of Mexican heritage. In fact, we don't know whether it's common among Latinos in Majorca, Dominican, and Puerto Rican ancestry because, in fact, we've never looked.

Now, these mutations are so prevalent among Ashkenazi Jews that typically we start off by screening Ashkenazi Jews for these three mutations because, by and large, they tend to account for 90% of the cases of breast and ovarian cancer. It is reasonable to start off screening Sephardic Jewish women for these mutations, but they're really not all-inclusive. There are other mutations that are common and specific to Sephardic Jewish populations that could be tested for. There are other mutations that occur, as well, which suggest that we should use the strategy of fully sequencing these genes in order to provide adequate risk assessment.

Dr. Oratz talked to you earlier about some of the risk factors that we know about for what increases a woman's risk for developing breast cancer, and they included such things as hormonal exposures and the time at which women first have children. We know some of this stuff from a study that we conducted several years ago among eight New York medical centers, along with Dr. Mary Claire King from the University of Washington. We learned that these risks of developing breast and ovarian cancer were, in fact, as high as you've actually seen in Jewish populations.

There is a study that's going on in Israel right now in which Ashkenazi Jewish men are being approached on the street and saying, "We're conducting a study. We'd like to learn more about the risks of developing breast and ovarian cancer if a woman inherits one of these mutations but doesn't necessarily come from a high-risk family." That's the reason for approaching men because, of course, the likelihood that they will have breast cancer themselves is pretty low and of course, they won't have ovarian cancer. Then similar to what occurred in the New York breast cancer study, the female relatives of the

men who were found to be carriers are contacted, and then their question would be, "Do you have a history of breast or ovarian cancer? Are you, in fact, a mutation carrier yourself?" The results of this study are suggesting that people who are identified through this population-based strategy seem to have risks that are pretty much the same as the people who are identified through family history.

Now, we're very interested in identifying what some of the genetic risk factors might be that might modify a woman's risk for developing breast and ovarian cancer. We've organized a study through NYU that we're planning to launch shortly because we've funded it with support from the Ginsburg Family Foundation and also from the Jewish Women's Foundation. We call it the Jewish Grandmothers Breast and Ovarian Cancer Study because we want to study older Jewish women. We want to identify Jewish women who have developed breast or ovarian cancer who may be BRCA1 or 2 mutation carriers, or may still come from high-risk families and don't have mutations in BRCA1 and 2.

We're also very keen on identifying these older Jewish women who fall into this 20 to 50% group that you've heard about who are mutation carriers but who never developed cancer. We believe that these women have had the very good fortune of carrying what we would call protective genes, and of course, these are the sort of genes that you want to bottle and you want to sell them to everybody because -- and I'm not being totally facetious about this -- because there may be something in these genes. There may be something in the variants of these genes that really tells us about something that can lead to the prevention of breast and ovarian cancer.

Most likely, you will be hearing about the Jewish Women's Breast and Ovarian Cancer Study from us over the course of the next several months because we plan to conduct a massive public education campaign about this so that we can encourage very widespread participation. Our goal for recruitment during the first year is to get the participation of 1,000 Jewish women.

I think this gives you a sense of what we're all about, and at this point, I will pass the mic on to Eillene.

IV. Presentation by Eillene Leistner

Eillene Leistner: Thank you so much. Good evening, everyone. I guess I can just reiterate my thanks to everyone here for joining us this evening. You've heard some very serious and yet very important information that I would hope you not only retain but you share with others. We have a gathering here, and we'd love to be able to spread the word to many more women in your community.

I wanted to thank again our presenters, Dr. Ruth Oratz, who is, in fact, a member of Sharsheret's Medical Advisory Board, and Dr. Harry Ostrer, and to our host, Eileen Kebasso and Sari Setton and Linda Eber. Thanks, also, again to Susan G. Komen for the Cure Greater New York City Affiliate. We could not do this program without you. Elana, thank you, also, very much for moderating our program and to MedStar for partnering.

As you heard, my name is Eillene Leistner, and I'm Executive Director of Sharsheret, which is a national organization of survivors. We're focused on supporting young Jewish women who are fighting breast cancer. Just some information on us -- since Sharsheret's inception in 2001, over 13,000 people have called or e-mailed us with their questions about a recent breast cancer diagnosis or their concerns about being at risk. Overwhelmingly, the calls have been from women who are from Ashkenazi backgrounds, and overwhelmingly, the genetics questions have related to the BRCA genetic mutation you heard about in our doctor's presentation. At the same time, we know that Sephardic women are being diagnosed with breast cancer and seem to have family histories of breast and ovarian cancer. The numbers of Sephardic women, though, who are calling Sharsheret regarding their diagnoses or their risks are very small compared to their Ashkenazi cousins.

We believe that breast cancer and its genetic risks are very openly discussed and receive increased media attention in the Ashkenazi Jewish community. Unfortunately, a lack of attention has been paid to the women of the Sephardic community. As a result, we believe that many women in the Sephardic community may not yet feel comfortable enough to speak about their needs openly. Our goal at Sharsheret is to lift the taboo that many women may feel, which restrains them from seeking the support they need by paying attention to the research and genetic studies that have been done in the Sephardic community. Ashkenazi women have benefited by the awareness, the open discussions, and the focus on their needs. It's your turn now.

Sharsheret believes that women in the Sephardi community are entitled to the same level of attention and a deeper understanding of the risks of their own genetic histories. As Dr. Oratz said, "Knowledge is power."

This symposium was our attempt to shed light on the needs of Sephardi women with breast cancer and/or with family histories of cancer, to open up the floodgates that have been holding women back from sharing their experiences, and to provide them with

opportunities for support through Sharsheret's programs. I'm going to tell you more about Sharsheret's program, but I hope that each one of you here will take an information packet that's on a seat next to you and give them to a friend or a relative and share what you've heard about tonight, with so many others, who really will benefit tremendously from hearing it, as well.

How can Sharsheret help Jewish women who are diagnosed with breast cancer? As you heard, the word Sharsheret means chain. It's a Hebrew word. We are a national nonprofit organization linking young Jewish women in their fight against breast cancer. We were founded to pair young Jewish women with volunteers who share their personal and medical experiences. Our mission is premised on the notion that oftentimes women who are diagnosed want to reach out to others who share not only their diagnoses but their life backgrounds. By the time women are diagnosed with cancer and are prepared to reach out for support, chances are they already have a medical team in place -- their oncologist, to whom they can ask treatment questions, a surgeon to address their medical concerns. What they are seeking, though, is a place to turn to for guidance, reassurance, a sense of community within the community, and Sharsheret is that place. Women from across the country have called Sharsheret to discuss the issues unique to Jewish women living with or facing breast cancer, and those concerns include an increased genetic risk of developing breast cancer. I just wanted to add a footnote here. I want to reiterate, we are talking about inherited breast cancer, but most breast cancer is not inherited. I'll say that again. 90% is not inherited.

I had breast cancer two years ago. No one in my family ever had breast cancer. And I did test for the gene, and I do not have it. It is most often the case that it is not inherited. What we are focusing on here is the unique circumstance of inherited genetics -- of inherited breast cancer and unique to the Jewish population. We want to study that in greater detail.

At Sharsheret, we're also concerned with the role of religion in daily life with cancer, the impact of cancer on religious rituals, and life with cancer in a close-knit community, life with cancer regarding fertility and childrearing, dating, and intimacy, and affected by all the treatment decisions.

Since our focus is heavily on young women, we were founded by a woman, Rochelle Shoretz, who discovered cancer in her own breast at the age of 28. We are focused on young women and the unique concerns that young women do face, but we don't turn away anyone who calls us.

In response to the needs of the women we serve, Sharsheret has launched several programs -- the *Link Program*, which is our core peer support network connecting women newly diagnosed or at high risk of developing breast cancer with others who share similar diagnoses and experiences. Their needs are individual and diverse. Our Link Program is completely confidential -- I say that again -- completely confidential. Sharing her appreciation for the Link Program, one caller wrote to us after her

treatment, "Even though my Link and I are in different parts of the country, I imagined her hand placed softly on my back as I entered the hospital for my surgery. It was a comfort that stayed with me throughout this ordeal."

Our *Embrace* program provides individual and group counseling for women with advanced stage or metastatic breast cancer. Our own clinician could not be here tonight because our Embrace group is meeting on a teleconference this evening.

Our *Empower* program, which provides individual and group support for predominantly young women without partners, single women with breast cancer, and we have women as young as 19 calling us.

Our *Genetics for Life* program, which is our newest program, which focuses on the concerns and issues related to hereditary breast cancer and women at risk. I want to mention that we do have a genetic counselor on staff now, so if you have questions and you don't want to go to a genetic counselor, you don't even know how to go to a genetic counselor, you can call Sharsheret to ask those preliminary questions so you can get the background information that will help guide you to that next step. We want to be there for you.

Sharsheret's *Quality of Life Programs* include the *Busy Box*, which you saw on the table outside, which provides resources for moms and activities for younger children to keep them busy while their mother is at the doctor or resting after treatment. And -- my little show and tell -- we have our *Best Face Forward* kit, which is filled with cosmetics and creams for women who are undergoing chemotherapy. Your body changes physically, and we try to make that a more satisfying time. We try to give a woman a sampling of cosmetics and much information to help her deal with the side effects of chemotherapy and radiation treatment.

Our *Education and Outreach Programs* include healthcare presentations like this evening's about the concerns of Jewish women facing breast cancer. Other Sharsheret symposia have addressed the subjects of breast cancer and fertility, parenting during breast cancer, Jewish family issues, preparing for the Jewish holidays, and surviving breast cancer.

Each and every one of the transcripts from these symposia, as well as this videotape, are on our website. They're easily accessible, and we can get them out to groups, as well.

Our *Sharsheret Supports*, trains individuals and organizations to set up Sharsheret-modeled support groups throughout the country, and new Sharsheret support programs are opening in Dallas, Texas; Greenwich, Connecticut; and Philadelphia, Pennsylvania. Our Sharsheret, the very -- the chain that we have, spans the country with over 550 links and callers who live in 35 states around the country, including Delta Junction, Alaska.

Through Sharsheret, thousands of individuals, family members, organizations, businesses, and health care professionals have been educated about the impact of breast cancer and men of our community. Sharsheret is bettering lives through programs that enhance the quality of life of women living with breast cancer, and empowering cancer survivors who join us as peer supporters. And Sharsheret is saving lives. We are generating conversations that encourage women to address their health needs, to access information about their own family histories, and to educate their own families with critical information about their well being.

So this is what you can do to help.

First, take care of yourself. That's why we have brought breast models, which we can show you, which you will even have the opportunity to practice a breast self-exam if you don't do it already, and to pose questions, medical questions, to our esteemed panelists.

Second, raise awareness by discussing with your sisters, mothers, daughters, aunts, and friends what you have learned tonight. Cancer has been a frightening subject in the history of all of our lives, and I'm sure people here still feel like for some, maybe it's the Big C. I grew up hearing about it like that. But I think that if we talk about it more openly and we get it out into the community and we discuss what our needs are, we have a greater likelihood of preventing and detecting early so that we are surviving longer and we are going to have a better life.

Third, we're going to ask you to take brochures, Sharsheret brochures, and information to your own doctors. When you go for your annual exams and your mammograms or anything, any gynecologist you go to, tell them you heard about Sharsheret so they can tell women who might be at risk or have been newly diagnosed. We need the word to get out, and your word is the strongest words that we can count on. The more you talk about breast cancer awareness, the more the community will feel comfortable addressing the needs of those in your own world facing this illness for now and in the future.

We hope that eventually they'll be able to bottle those genes that Dr. Ostrer talked about that could protect all of us in the future, and they are discovering and working on so much phenomenal research, and so many new medications have come down the pipeline that are helping women get through this illness. But when I hear Dr. Oratz say that 40,000 women will still die from this disease every year, that's a heartbreak. That's a heartbreak because many of them are dying because the illness is not being detected early enough because they are not doing what they could for themselves.

So we hope that this Sharsheret symposium has empowered you to live better and healthier lives. Thank you so much again for joining us this evening. Have a good night.

V. Question and Answer Session

Elana Silber: Thank you, Eillene and the doctors. It was very informative, very empowering. I felt that excitement that we feel every day at Sharsheret to go out there and help the women around us.

In advance of tonight, we had a question someone sent in. "If a Jewish woman of Sephardi descent wanted to contact someone to participate in research on studies of Sephardic Jewish women, how do they get that information? How can they participate? Who would they call? Can they call you? How does it work?"

Dr. Harry Ostrer: They certainly can call me. We will have a genetic counselor who is dedicated to the study. I can give you a name and telephone number now if you would like. Our genetic counselor's name is Feighanne Hathaway, and her telephone number is 212-731-5104.

Someone asked a question, "Is a mammogram alone sufficient? Why are you recommending ultrasound and MRI, as well?"

Dr. Ruth Oratz: For women who are not at very increased risk of breast cancer, for the average American woman, the guideline recommendation from the American Cancer Society and from the American Society of Clinical Oncologists is for annual screening mammography over age 50 and for mammograms, every one to two years over age 40. However, about 15% of the time, mammograms will not detect breast cancer. We have learned, especially in younger women under the age of 50 or women in whom the mammogram picture shows very dense breast tissue, that we should use an additional modality, whether that's ultrasound or MRI, for screening.

In women who we know have a genetic mutation in BRCA1 or BRCA2, whether they've already developed one breast cancer that we've treated and then we're following them going forward, or if that woman has never developed cancer and we're screening her, that mammograms alone are probably not sufficient. In that group of women who have mutations, we do recommend adding ultrasound and/or MRI, and those recommendations are made on an individual case-by-case basis. But the American Society of Clinical Oncology just this year changed their guidelines for women who are known to be mutation carriers to increased surveillance with these modalities. That's not to say that older women should not also have ultrasounds or MRIs, and that decision is made, I think, on a case-by-case basis with your physician, particularly if there's any question at all that the mammogram may be abnormal, that it may not correspond to what we find on physical examination. Some women have really lumpy breasts, and the mammogram may not show us what we need to see. Ultrasounds and MRI can be very helpful in that situation.

Unidentified Audience Participant: Is that also with a gynecological test? Should you also have a sonogram, ask your gynecologist to do that?

Dr. Ruth Oratz: Yes. Screening for GYN malignancies -- ovarian cancer and uterine cancer -- is much more problematic. Certainly, for women, we recommend all women should have a GYN examination at least once a year with a pap smear. Pap smears give us a lot of information about cervical cancer and about possibly uterine cancer, as well.

And I'm just going to take a little aside here to just bring up another whole topic not related to BRCA1 or BRCA2, but pap smears tell us, and we've learned, that cervical cancer is related in many cases to an infection from a virus called human papillomavirus. This virus is very, very, very common. Most of us have been exposed to it. In some women who have been exposed to human papillomavirus virus, that can lead to the development of cervical cancer. There is now a vaccine that has been tested and approved to immunize young women and young men, boys, as well, because that's how the virus gets passed, through contact. Before these young men and women become sexually active, they should be immunized to protect them against infection from this virus. In women, that will have a significant impact in reducing the risk of cervical cancer. If we immunize boys, we'll cut down on the risk of passing that virus because of sexual contact. There is a very, very rare incidence of cancer of the penis and also of other diseases that can be caused by this virus; in particular, genital warts. That's an aside. It's not related to BRCA mutations, but you should talk to your gynecologists and think about having young women screened to see whether or not they've been exposed to HPV and for young girls before they become sexually active, adolescents, not little girls, 11, 12, 13, 14, speak to your pediatricians and get information about how you can protect these girls.

Unidentified Audience Participant: I think that pediatricians have to be educated on this.

Dr. Ruth Oratz: We all need some more experience with this. This is very new. It's very, very new, but there is, I think, very good scientific data. These studies were very well conducted, and we can, with a vaccine, prevent a cancer that really is quite debilitating, not as common in the Jewish population as other cancers, but nonetheless, women do get cervical cancer.

Coming back to your question about GYN screening, pap smear helps for cervical cancer and perhaps uterine cancer. Screening for ovarian cancer is very problematic and very difficult. Pelvic ultrasound is a great test on the day it's performed.

Unidentified Audience Participant: What does that mean?

Dr. Ruth Oratz: That means that a month later, something could be going on that we didn't see on that ultrasound from a few weeks ago.

Unidentified Audience Participant: But that's the same thing with a mammogram.

Dr. Ruth Oratz: You know, with mammography, it's rare that we miss a breast cancer. It's rare that we don't detect a breast cancer, what we call an interval cancer. If someone is going every year for her exam and her mammogram and, if necessary, that ultrasound and MRI, we're pretty good at early detection with mammography. We're very good at it.

Unidentified Audience Participant: Isn't there a breast cancer that the tumor grows very rapidly?

Dr. Ruth Oratz: Yes, there are. As I mentioned, breast cancer is not just one disease. There are some types of breast cancer that do develop very quickly and from one year to the next will show up. It wasn't present on last year's mammogram, and then three or four months later, boom, there's a big tumor in the breast. That's a different type of breast cancer and much less common but may be associated, in fact, with mutations in BRCA1. They may be associated with these more aggressive types of breast cancer, another reason for screening and enhanced surveillance in women who are risk for inherited predisposition to breast cancer.

There is a lot of research being done now to try and find better screening tests for ovarian cancer, and in fact, we are encouraged by a recent publication where the investigators identified not just one sera marker but a mixture of five or six different factors in a blood test that, when combined together, may be a much better screening test for early-stage ovarian cancer. This is brand new research that's just been published, and we need to have more work in this area to validate that test, as well as developing other tests. But this is a major priority in women's health care.

Unidentified Audience Participant: They're also saying that if you have bloating in the abdomen or maybe you've lost weight, there are other things that seem innocent enough that may be a symptom. Maybe you'd want to talk about those?

Dr. Ruth Oratz: Yes, you're absolutely correct. For any woman, particularly over the age of 40, ovarian cancer is rare in younger women but sometimes occurs -- but in women over the age of 40, funny, weird symptoms -- bloating, constipation, abdominal pain, something just doesn't feel right -- go to your doctor.

I think that we're used to being uncomfortable a lot of the time. I know a lot of the time we walk around with aches and pains, and every month we have aches and pains. We're used to that. But if something persists, don't ignore it. You're not being a hypochondriac. You're not being an alarmist. If you have a symptom that wasn't there before and you're concerned about it, bring it to your doctor's attention. See your gynecologist, see your internist, and make sure that it's followed up and evaluated carefully. That's very important.

Unidentified Audience Participant: A first-degree relative with cancer in the right leg, does that also apply to any type of cancer -- lung cancer, liver cancer?

Dr. Ruth Oratz: That's a good question.

Dr. Harry Ostrer: The question is, if you have a first-degree relative with any cancer, are you at increased risk for cancer? I have to say the answer to that question is no. Some questions tend to have a familiar and genetic basis, and others really don't. You asked about liver and lung cancer in particular, and both of those forms of cancer really don't tend to have a genetic basis, aren't associated with genetic syndromes, and so we wouldn't necessarily recommend that the first-degree relatives of someone with one of those cancers should consult with a medical geneticist.

Unidentified Audience Participant: You wouldn't recommend?

Dr. Harry Ostrer: Would not recommend, correct.

Unidentified Audience Participant: But if it's more than one person, two or three, would that increase the rate or not?

Dr. Harry Ostrer: Typically as you've seen, having more first-degree relatives will point to a familial basis for cancer. There are rare families which seem to have a familial form of lung cancer. We don't really understand what the genetic basis is for that yet. There are Chinese families that have multiple cases of liver cancer, but that really seems to be on the basis of infection with hepatitis B virus rather than having a genetic predisposition.

But if you have questions, give us a call, as we've said, we don't want to discuss people's personal circumstances tonight because we want to protect their privacy, but give us a call, and we'll tell you whether a consultation is appropriate. We get these calls every single day, "What do you think, should we come to see you?" Sometimes we'll say yes, and sometimes we'll say no, and it will be based on reasoning that's associated with what you tell us.

Dr. Ruth Oratz: Let me just add that we do see some cancers that cluster together. Breast and ovarian certainly cluster together. In some of those families, we also see pancreatic and prostate cancer with breast and ovarian. That is linked with the BRCA mutations. In some families, we see a lot of colorectal cancer, GI cancers, and there may be in some of those families a familial link to that.

Dr. Harry Ostrer: And it may be associated with uterine cancer.

Dr. Ruth Oratz: And that may also be associated with uterine cancer or sarcoma. There's another syndrome where we see thyroid linked with breast cancer. It really depends on what's going on in the family. You can also call Sharsheret. And as you heard tonight, there is a genetic counselor available to you at Sharsheret who can go through some preliminary information with you and then help you determine whether or not referral to a genetic counselor or a medical geneticist is appropriate.

Unidentified Audience Participant: How much does genetic testing cost?

Dr. Harry Ostrer: It depends what's done. The full sequencing for BRCA1 and 2 costs about \$3,000, and it's because there's this one company that holds the patent for testing, and they enforce it pretty strictly.

Unidentified Audience Participant: It's not covered by insurance?

Dr. Harry Ostrer: It is very commonly covered by insurance.

Eillene Leistner: I'll share with you my experience. If you are diagnosed with a breast cancer, you are considered to be, as Dr. Oratz and Dr. Ostrer said, at higher risk, so even if there isn't a family history. In my case, and I just share this with you to help maybe open up some doors in your own mind, my father was a survivor of the Holocaust and all of his family perished, so we didn't have any records, any knowledge of anyone in his family. There was a whole side of my family that was a blank slate. We didn't know.

When I was considering the testing, I had to approach my doctor and say, "Do you think this is something that is warranted?" and they said, "Yes, speak with a genetic counselor." At the time, we didn't have someone on staff. I went to a genetic counselor. I had a session with the genetic counselor for an hour. We met. She herself is a doctor, as well. And we talked about insurance and coverage and all that, she was able to submit to my insurance company to see if I was eligible and if I would be covered given the factors that were particular to my life, and they covered the entire test.

I had the two levels of the screening, which is the preliminary level, which costs \$400, which is focused mostly on the BRCA genetic mutation. Then they do a much more extensive screening, that's the sequencing, which is several thousand dollars. In my case, the whole thing was covered.

And I think -- I want to just also emphasize that it's not just New York State that has laws that protect the individual. It's New Jersey, but it is also individual states have different laws, and the genetics counselors in each state will be able to answer those kinds of questions for you. At Sharsheret, we can look this information up. We can refer you to other people, other organizations that also focus exclusively on genetics, and we will be there to help you come through this.

Also, one other thing. I just wanted to emphasize one other point. I don't know if you heard this, but men carry the BRCA gene as well as women. I think we all grew up with the myth that this is a genetic carrier that only happens in women, but it's not. If you have family members who have had prostate cancer or especially men in your family who have had breast cancer, you are at higher risk.

Dr. Ruth Oratz: Actually, on the drive over this evening, Dr. Ostrer and I were talking about a colleague and friend of ours, and this gentleman came up to me one afternoon in the hospital, oh, more than 10 years ago, and said, "I have three first cousins who had ovarian cancer, and I just heard about this new gene that may be linked to ovarian and breast cancer." He was healthy, but he had these three first cousins with ovarian cancer, and he had two daughters. He was very concerned to find out whether or not there was a genetic mutation in his family. And we pursued that and indeed learned that he was a carrier of a genetic mutation. Then other individuals in his family were tested, and we were able to learn who did and who did not carry the gene. For any individual who carries a mutation in BRCA1 or BRCA2, each child, whether it's a boy or a girl, has a 50/50 chance of inheriting that mutation, and men can, in turn, pass that on to their children. So as Eillene is saying, this can pass through men or through women.

Unidentified Audience Participant: On that note, if there is a family carrier, a known carrier, do they have to be very careful to be married if they have very similar backgrounds?

Dr. Ruth Oratz: The question is about marriage, if we're concerned that a young man and woman would get married and both potentially carry this genetic mutation. That's a complicated question. I am going to let Harry answer that. It's a very complicated question.

Dr. Harry Ostrer: One thing that's significant, though, is you might say, well, gee, what happens if a man and a woman both carry a mutation in BRCA1 or if they both carry mutation in BRCA2? And we don't know of any individuals who carry two mutations in BRCA1. It just doesn't happen. And the reason for that is that we think that it's lethal in the embryos, that embryos that are homozygous, if you will, for mutations in BRCA1 don't survive and aren't carried to term.

What happens if the individual carries a mutation in BRCA1 and BRCA2? And their risks, in fact, don't seem to be greater than those of someone who carries a mutation either in BRCA1 or BRCA2.

Now, the issue with the children of parents who both carry mutations in BRCA2 is really quite interesting because about 25% of the time, the children are at risk for developing a condition that's called Fanconi anemia. This is a birth defect, and it's associated with a blood disorder, as the name implies, a short stature and markedly increased risk for developing cancers, not only breast and ovarian cancer but also childhood leukemias and lymphomas.

It's raised the question of, well, gee, should we be offering screening for BRCA2 in the Ashkenazi Jewish and Sephardic populations? We haven't really reached a consensus about that yet.

Dr. Ruth Oratz: I also want to remind you that although we're talking tonight about inherited cancer syndromes, 90% of women who develop breast cancer have no genetic susceptibility, at least that's been identified. And just coming from a family where someone has had breast cancer should not stigmatize other members of that family in any way in terms of saying there's an increased risk and, therefore, that person may not be a good marriage partner.

Karen David: My name is Karen David. I'm a medical geneticist in Brooklyn, in a Methodist hospital in Brooklyn. You've really given an excellent, excellent presentation. I just want to congratulate you.

Dr. Harry Ostrer: Thank you.

Karen David: I want to add, also, that Myriad Genetics, which is the laboratory that holds that famous patent, they do have a hardship program. If people do not have insurance or with certain financial screening, they will provide all \$3,000 for free. I don't think that people who may feel they want testing and are at a significant risk to find a mutation should automatically discount because they don't have insurance. Myriad might pay.

Dr. Harry Ostrer: Yes, thanks for pointing that out, Karen.

Unidentified Audience Participant: What I think I'm hearing you say, and correct me if I'm wrong, is there really isn't a difference in terms of the mutations between Ashkenazi and Sephardic women. It's just that we hear about it more in Ashkenazi women.

Dr. Ruth Oratz: Well, and because the original studies that were done to help identify these mutations were done in Ashkenazi populations because there were more Ashkenazi Jews in those cities where the original research was being conducted. But as we're branching out, both in Israel and in the United States, with research and looking at other Jewish populations of different origin geographically and perhaps -- you know, we think we're all related really.

Dr. Harry Ostrer: Six degrees of separation.

Dr. Ruth Oratz: We are seeing these mutations in Sephardic populations, also, and we feel that women who are at risk for genetic cancer syndromes should be screened and counseled in the same way.

Unidentified Audience Participant: In a pedigree where you have a significant number of first cousins that are all showing up with breast cancer and none of them are testing for those mutations, it would suggest that there's some gene that's not found or some mutation that's not found. I mean especially if over 90% of the women are not carrying the gene and are still coming up with breast cancer.

Dr. Harry Ostrer: Absolutely no question about that, and so that is a very hot topic of investigation for us and the study that we're organizing, as well as studies that are taking place elsewhere.

There are some other genetic risk factors that have been identified, but it's really getting into a level of detail that would require a fair amount of time right now that we might not want to discuss. Those aren't what we would call high-penetrance risk factors, where if you get one of them, that your likelihood for developing breast or ovarian cancer is on the order of what you see with BRCA1 and 2, so this 40 to 80% range.

People have done a lot of work looking for a BRCA3, and it really hasn't been found so far. There's also the possibility that if you come from a high-risk family and BRCA1 and 2 are tested, there may still be something else going on with those genes that hasn't been identified yet. As new technologies come along, even with BRCA1 and 2, we incorporate those technologies into the testing strategy.

For instance, deletions of BRCA1 and 2 were identified as relatively common causes of heritable breast and ovarian cancer, accounting for perhaps 1.5% of the total, and now Mary has added those to their panel after we banged them over the head that they should do it.

Unidentified Audience Participant: What do you say when four out of nine women, first cousins in a family, have breast cancer, so that's like almost 50%, and then they all have daughters, but none of them tested positive? So what about their daughters?

Dr. Ruth Oratz: She's saying they tested -- they tested negative?

Dr. Harry Ostrer: And they had sequencing and they had deletion tests?

Dr. Ruth Oratz: They had all those?

Unidentified Audience Participant: Complete screening.

Dr. Harry Ostrer: They're from one of these high-risk families for which we haven't identified a mutation yet. The risk doesn't drop because the test was negative. We still call those high-risk people, and we take that very seriously, and we talk about the increased surveillance, and we talk about the other preventive strategies, and some of those people will decide that they want to have risk-reducing surgery because we don't have anything else to offer to them. In fact, that's what women did before we had testing for BRCA1 and 2. For those of us who have been practicing throughout this era, we remember that very well.

Dr. Ruth Oratz: In fact, one of the earliest studies that was done that gave us supportive evidence that there were genes involved in breast cancer was a study done, I believe at Memorial, of women who had breast cancer and their sisters. And the

sisters of women who were diagnosed were offered the option -- this goes back 20 years ago or more -- the option of having prophylactic mastectomy. There was no genetic screening or testing. We had no idea what the genes were. Those sisters who did not have breast cancer were then followed, and it turned out that in the group of sisters who decided to have mastectomy, compared to the group who did not, there was a difference in the incidence of breast cancer, and that some of the sisters who did not have mastectomies did develop cancers. More of them developed cancers than women who did not have sisters with breast cancer. So there were these early hints.

Coming back to your question, if we test a family and we do not find a genetic mutation but we think it's a high-risk family, we will use the same follow-up screening and surveillance criteria. We'll watch very, very closely.

Unidentified Audience Participant: Should those daughters start younger than they normally would go for mammography?

Dr. Ruth Oratz: They should speak to a physician who's an expert in this area who can help to develop an appropriate screening program for them, which probably is going to be more than annual mammograms, yes.

Unidentified Audience Participant: Yes. How much longer does Myriad have the patent?

Dr. Harry Ostrer: That's an excellent question, and they actually have more than one patent, so they have a series of interlocking patents. Although the patent on BRCA1 should expire in 2011, there are other patents, as well, on the method of genetic testing, and so they're going to be pursuing this as long as they can. I think it'll probably go until 2017.

I had a discussion with some lawyers from the ACLU about their patent. I've done some work with them in the past. I said, "Well, what if we offer free testing? Is that considered to be a patent infringement?" And because we're a genetic testing program and genetic testing laboratory, in fact, it might be deemed patent infringement because we're using free testing as an inducement for people to obtain other services from us. And it could be court tested, but we haven't done that so far.

Elana Silber: Thank you and good night.

VI. Speakers' Bios

Eillene Leistner, Executive Director, Sharsheret, joined the staff in March 2007 and with the Board of Directors is responsible for Sharsheret's overall operations, ensuring its fiscal standing, implementing its mission and advancing its growth and development. Ms. Leistner is a recent breast cancer survivor. Ms. Leistner earned a bachelor of arts in English Literature from Lehman College and a master's degree in English Literature from Northwestern University. She has completed the Executive Management Institute program for not-for-profit executives of the Owen Graduate School of Management, Vanderbilt University.

Ruth Oratz, M.D. is Associate Professor of Clinical Medicine at the New York University School of Medicine. Dr. Oratz is the Founder and Director of The Women's Oncology & Wellness Practice in New York City and specializes in treating women with breast cancer and other malignancies, and those at risk for cancer. Dr. Oratz was named "Physician of the Year" by CancerCare in 2005. Dr. Oratz has been listed in "The Best Doctors in America" in *Redbook Magazine* and "The Best Doctors in NYC" in *New York Magazine*. Dr. Oratz is especially committed to helping the woman with cancer continue to live her life actively and fully, placing significant attention on flexible treatment programs that comprehensively address a woman's personal needs, including career, family life, and sexuality.

Harry Ostrer, M.D. is Professor of Pediatrics, Pathology, and Medicine and Director of the Human Genetics Program in the Department of Pediatrics at New York University School of Medicine. As Director of the Molecular Genetics Laboratory of NYU School of Medicine, he has pioneered with the introduction of many new tests into clinical practice and has demonstrated that multiplex genetic testing is safe and widely accepted by the Ashkenazi Jewish population. He is the author of over 100 original research and review articles and the book, *Non-Mendelian Genetics in Humans* (Oxford University Press, 1998). He is currently completing a book on Jewish history and genetics. He has been concerned about fairness in the use of genetic information and has served on a multitude of advisory panels. Dr. Ostrer has received awards from Rensselaer Polytechnic Institute, March of Dimes Birth Defects Foundation, Skin Cancer Foundation and Weizmann Institute of Science.

VII. 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 by telephone and online on the *Sharsheret Forum*.
- **Education and Outreach Programs**, including health care symposia addressing the concerns of young women facing breast cancer, *Sharsheret Supports*, a national model for local support groups, and *Family Focus*, a program for caregivers and family members.
- **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, *Empower*, for single women facing breast cancer, *Genetics for Life* to focus on concerns and issues relating to hereditary breast cancer, and *Embrace*, a support program for 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 Greater New York City Affiliate of
Susan G. Komen For The Cure

VIII. Symposium Slide Show

To view the slideshow presentation, go to:

<http://www.sharsheret.org/library/SephardicSymposiumPowerpoint.pps>

IX. Disclaimer

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