Hereditary Breast and Ovarian Cancer [1]

What is Hereditary Breast and Ovarian Cancer?

Hereditary Breast and Ovarian Cancer (HBOC) should be considered when there are multiple cases of breast cancer [2] and/or ovarian cancer [3] on the same side of the family. The chance that a family has HBOC increases in any of these situations:

- One or more women are diagnosed at age 45 or younger
- One or more women are diagnosed with breast cancer before age 50 with additional family history of cancer, such as prostate cancer [4], melanoma [5], and pancreatic cancer [6]
- There is breast or ovarian cancer in multiple generations on the same side of the family, such as having both a grandmother and an aunt on your father?s side diagnosed
- A woman is diagnosed with a second breast cancer in the same or the other breast or has both breast and ovarian cancers
- A male relative is diagnosed with breast cancer [7]
- There is a history of breast cancer or ovarian cancer and pancreatic cancer on the same side of the family
- There is a history of breast and/or ovarian, pancreatic, or male breast cancer in a family of Ashkenazi Jewish ancestry

What causes HBOC?

HBOC is an inherited genetic condition. This means that the cancer risk is passed from generation to generation in a family. Two genes are associated with the majority of HBOC: *BRCA1* and *BRCA2* (BRCA stands for BReast CAncer). Other less common genes have also been associated with an increased risk of developing breast and other cancers, such as mutations in the *TP53, PTEN, CDH1, ATM, CHEK2 or PALB2* tumor suppression genes and many others. Blood tests now include many of these genes in a single, multigene test. A mutation (alteration) in either *BRCA1* or *BRCA2* gives a woman an increased lifetime risk of developing breast and ovarian cancers. Men with these gene mutations also have an increased risk of breast cancer and prostate cancer. Not all families with multiple cases of breast and ovarian cancer have mutations in *BRCA1* or *BRCA2*.

How is HBOC inherited?

Normally, every cell has two copies of each gene: one inherited from the mother and one

inherited from the father. HBOC follows an autosomal dominant inheritance pattern, in which a mutation needs to happen in only one copy of the gene for the person to have an increased risk of getting that disease. This means that a parent with a gene mutation may pass along a copy of their normal gene or a copy of the gene with the mutation. Therefore, a child who has a parent with a mutation has a 50% chance of inheriting that mutation. A brother, sister, or parent of a person who has a mutation also has a 50% chance of having the same mutation.

Options exist for couples interested in having a child when they know that one of them carries a gene mutation that increases the risk for this hereditary cancer syndrome. Preimplantation Genetic Diagnosis (PGD) is a medical procedure done in conjunction with in-vitro fertilization (IVF). It allows both women and men who carry a specific known genetic mutation to have children who do not carry the mutation. A woman?s eggs are removed and then fertilized (in a laboratory setting) with sperm. When the embryos reach a certain size, one cell is removed and is tested for the hereditary condition in question. The parents can then choose to transfer the embryos without the mutation to the woman?s uterus. PGD has been in use for over a decade, and more recently has been used for several hereditary cancer predisposition syndromes. For more information, talk with an assisted reproduction specialist at a fertility clinic.

How common is HBOC?

Most breast [2] and ovarian [3] cancers are sporadic, meaning they occur by chance with no known cause. Most women who have breast or ovarian cancer do not have HBOC.

Current estimates are that less than 1% of the general population has a mutation in the *BRCA1* or *BRCA2* genes, and only 10% to 15% of women diagnosed with breast cancer have a mutation in one of these genes. Nine to 28% of women under the age of 60 diagnosed with ?triple negative? breast cancer, which are cancers that do not have receptors for estrogen, progesterone and HER2/neu [8], will have a *BRCA1* gene mutation; therefore international guidelines recommend that these women be referred for genetic counseling and genetic testing (see below). HBOC is most frequently diagnosed when there are multiple cases of breast cancer and/or ovarian cancer on the same side of the family. In families with four or more cases of breast cancer diagnosed before age 60, the chance of HBOC is approximately 80%. To compare, the chance of finding HBOC when only one woman has had breast cancer diagnosed under age 50 is estimated to be 10% or less.

Individuals with Ashkenazi Jewish ancestry have an increased chance of having HBOC. Three specific gene mutations are common in this population:

- 185delAG in *BRCA1* (also reported as 187delAG)
- 5382insC in *BRCA1*
- 6174delT in *BRCA2*

It is estimated that about one in 40 individuals with Ashkenazi Jewish ancestry has one of these three mutations. Approximately one in 10 women with breast cancer and one in three women with ovarian cancer in Ashkenazi Jewish families have one of the *BRCA1* or *BRCA2* gene mutations. If a person is found to have a *BRCA2* mutation, it is important for their partner to also be tested prior to pregnancy. This is particularly true for those of Ashkenazi Jewish ancestry where the risk of having the mutation is higher (see next section). If both parents carry a *BRCA2*

gene mutation, there is a 25% risk with each pregnancy of having a child with Fanconi anemia, which is an inherited disorder, associated with physical abnormalities, an increased risk of blood cancers, and other serious problems. Fanconi anemia is inherited in an autosomal recessive pattern, meaning that if a child inherits two copies of the *BRCA2* gene with a mutation (one from each parent) they will be born with the disease.

For women without a previous diagnosis of breast or ovarian cancer, the U.S. Preventive Services Task Force (USPSTF) provides recommendations regarding whether or not genetic counseling and testing is recommended. These recommendations, summarized below, are available on the USPSTF website, http://www.uspreventiveservicestaskforce.org/uspstf/uspsbrgen.htm [9]. The phrase ?first-degree relatives? include parents, siblings, and children. ?Second-degree relatives? include aunts/uncles, grandparents, grandchildren, and nieces/nephews.

- Both maternal (mother?s) and paternal (father?s) family medical histories are important
- For non?Ashkenazi Jewish women:
  - Two first-degree relatives with breast cancer, one with a diagnosis at age 50 or younger
  - A combination of three or more first- or second-degree relatives with breast cancer regardless of age at diagnosis
  - A combination of both breast and ovarian cancer among first- and second- degree relatives
  - A first-degree relative with bilateral breast cancer (cancer in both breasts)
  - A combination of two or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis
  - A first- or second-degree relative with both breast and ovarian cancer at any age
  - A history of breast cancer in a male relative
- For women of Ashkenazi Jewish heritage, an increased-risk includes:
  - Any first-degree relative or two second-degree relatives on the same side of the family with breast or ovarian cancer.
  - About 2% of adult women in the general population have a risk of developing breast cancer.
  - Women with none of these family history patterns have a low probability of having a mutation in *BRCA1* or *BRCA2* genes.

How is Hereditary Breast and Ovarian Cancer (HBOC) identified?

Families with multiple women diagnosed with breast cancer before age 50 and families with both breast and ovarian cancers might be at risk for having HBOC. Mutations in the *BRCA1* or *BRCA2* genes can be identified through a blood or saliva test. Since most breast and ovarian cancers are sporadic, meaning it occurs by chance with no known cause, genetic testing is recommended primarily for people who have a personal and/or family history that suggests HBOC. While standard gene sequencing identifies the majority of mutations, there are other types of mutations called rearrangements, which are also called deletions or duplications, in *BRCA1* and *BRCA2* that also may cause an increased risk for these cancers. Testing for large rearrangements in *BRCA1* and *BRCA2* is now available. If the result of your initial *BRCA1* and *BRCA2* genetic testing was negative, meaning no mutation was detected, or a variant of uncertain significance was identified, there may be additional testing that is recommended. Talk with your doctor or

genetic counselor for more information. Most, but not all, insurance companies are now covering the cost of complete *BRCA1* and *BRCA2* testing, including Medicare and Medicaid. Many genetic specialists are now offering testing that includes multigene panels and may offer additional insight. These tests may include 6, 20, or 40 genes depending on the personal and family history. The multigene tests may often be ordered at the same time as *BRCA1* and *BRCA2* testing. You may want to discuss this information with your genetic counselor for complete information. If a mutation is identified in one of the other genes that increase risk for breast, ovarian and other cancers, then a tailored surveillance plan will be developed based on the pattern of cancers associated with the specific gene and family history of cancer.

However, women under the age of 60 with ?triple negative? breast cancer (see above; estrogen receptor, progesterone receptor, and HER2 negative) are at risk of having a *BRCA1* mutation, regardless of family history.

Testing for mutations in the *BRCA1* or *BRCA2* genes may not be beneficial for the average woman.

What are the estimated cancer risks associated with HBOC?

Cancer risks for women with HBOC

- Lifetime risk of breast cancer 50% to 85%
- Risk of breast cancer before age 50 30% to 50%
- Lifetime risk of ovarian cancer
  - *BRCA1* gene mutation 25% to 50%
  - *BRCA2* gene mutation 15% to 30%
- Developing a second breast cancer 40% to 60% (the risk of breast cancer occurring in the other breast rises approximately 2% to 3% per year)

Cancer risks for men with HBOC

- Lifetime risk of breast cancer
  - *BRCA1* gene mutation 1% to 2% (10-fold increase over the general population)
  - *BRCA2* gene mutation 6%
- Risk of prostate cancer
  - *BRCA1* gene mutation some increased risk
  - *BRCA2* gene mutation 20%
- Men with a *BRCA2* gene mutation have a significantly increased risk of developing more aggressive prostate cancer before age 65 and therefore screening should begin at age 40.

Breast cancer subtypes and inherited mutations

Cancers diagnosed in individuals with *BRCA* mutations often have specific characteristics:

- 80% to 90% of the breast cancers in women with a *BRCA1* mutation are ?triple negative?, as discussed above

- 80% of the breast cancer in women with a *BRCA2* mutation are estrogen receptor positive, progesterone receptor positive, and HER2/neu negative

Other cancer risks for people with HBOC

Both men and women with mutations in the *BRCA2* gene may be at an increased risk of other types of cancer, including melanoma [5] and pancreatic [6], stomach [10], esophageal [11], and bile duct [12] cancers. Rare mutations in other genes may be associated with an increased risk of developing breast and other cancers, including the Li-Fraumeni syndrome [13] (*TP53* gene), Cowden syndrome [14] (*PTEN* gene), and others. The pattern of cancers in the family is often a clue to the specific gene that may explain the hereditary cancer for that family. Recently, new panels of multiple genes have been developed for testing in a patient with a strong personal and family history. Multigene panel tests include *BRCA1* and *BRCA2* and many other genes that increase the risk of breast, ovarian and other cancers. If an individual has a negative test result for *BRCA1* and *BRCA2*, then mutations in other genes may or may not be present. New testing technology -- sometimes referred to as ?next generation sequencing,? ?massively parallel sequencing,? or ?deep sequencing? -- has made it faster and less expensive to test for mutations in multiple genes at the same time. If a genetic mutation is found, this could explain the cancers in a specific family and provide information about which family members are at risk and what type of monitoring and prevention/risk-reduction methods are appropriate.

Risk-reduction - What can I do to reduce my risk of developing cancer of the breast or ovary if I have a*BRCA* gene mutation?

Risk-reducing surgery

A risk-reducing, bilateral mastectomy, which is the removal of the breast tissue from both breasts, can reduce the risk of breast cancer by more than 90%. Only about 3% of breast cancers associated with *BRCA* mutations are diagnosed before age 30, so surgery could be considered over the age of 30 for most women.

Risk-reducing salpingo-oophorectomy, which is the removal of the ovaries and fallopian tubes, can reduce the risk of ovarian cancer by approximately 90%. If this surgery is completed in premenopausal women, it is also associated with a 50% decrease in breast cancer risk. A special procedure to look for microscopic cancer in the ovaries and fallopian tubes is recommended following this procedure

Deciding whether or not to have surgery to reduce your risk of developing breast or ovarian cancer is a very personal decision. Your doctor and genetic counselor can help you understand the risks and benefits, based on your health, *BRCA* status, and family history of cancer.

Prophylaxis/chemoprevention

Tamoxifen (Nolvadex, Soltamox) taken for five years by individuals with *BRCA2* mutations reduces the risk of breast cancer by 50%. There is less data regarding the impact of tamoxifen in those with *BRCA1* mutations, as tamoxifen is less likely to reduce the risk of developing a ?triple negative? breast cancer.

Oral contraceptives (birth control pills) taken for five years by individuals with *BRCA1* or *BRCA2* mutations may be associated with a decreased risk of ovarian cancer by approximately 50%. This is recommended in the late 20?s or 30?s and must be balanced by a potential slight increase in the risk of breast cancer.

Screening - What are the screening options for HBOC?

It is important to talk with your doctor about the following screening options, as each individual is different:

Screening for women with a*BRCA1* or*BRCA2* gene mutation

- Monthly breast self-examinations, beginning at age 18
- Bi-yearly clinical breast examinations (examination performed twice a year by a doctor or nurse), beginning between the ages of 25 to 30
- Yearly magnetic resonance imaging (MRI) scans of both breasts, beginning at age 25
- Yearly MRI alternating every 6 months with mammograms, beginning at age 30
- Pelvic examination, trans-vaginal ultrasound [15] with color doppler, and CA-125 blood test every 6 months, beginning at age 30
- Consideration for risk reducing salpingo-oophorectomy (removal of ovaries and fallopian tubes) by age 35 or once child-bearing is complete (screening for ovarian cancer is not yet able to identify the majority of early cancers)

Screening for men

- Monthly breast self-examinations, beginning around age 30
- Yearly clinical breast examinations, beginning around age 30
- Baseline mammogram at age 35 for men with a *BRCA2* gene mutation
- Yearly prostate cancer screening [16] with digital rectal exam and PSA blood test, beginning at age 40. Current USPSTF guidelines for men recommend reducing the use of PSA screening do not alter the recommendation for annual and early PSA screening for men with a *BRCA1* or *BRCA2* gene mutation.

Screening options may change over time as new technologies are developed and more is learned about HBOC. It is important to talk with your doctor about appropriate screening tests for you.

Learn more about what to expect when having common tests, procedures, and scans [17].

Questions to ask the doctor

If you are concerned about your risk of breast cancer [2] or ovarian cancer [3], talk with your doctor. Consider asking the following questions of your doctor:

- What is my risk of developing breast and ovarian cancers?
- What can I do to reduce my risk of cancer [18]?
- What are my options for cancer screening?

If you are concerned about your family history and think your family may have HBOC, consider asking the following questions:

- Does my family history increase my risk of breast cancer or ovarian cancer?
- Should I meet with a genetic counselor?
- Should I consider genetic testing [19]?

Additional resources

Guide to Breast Cancer [2]

Guide to Male Breast Cancer [7]

Guide to Ovarian Cancer [3]

Guide to Prostate Cancer [4]

What to Expect When You Meet with a Genetic Counselor [20]

National Comprehensive Cancer Network - Guidelines for Patients
www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf [21]

Facing Our Risk of Cancer Empowered (FORCE)
www.facingourrisk.org [22]

Young Survival Coalition
www.youngsurvival.org [23]

National Ovarian Cancer Coalition
www.ovarian.org [24]

Foundation for Women?s Cancers
http://www.foundationforwomenscancer.org/ [25]

National Cancer Institute
www.cancer.gov [26]

American Cancer Society
www.cancer.org [27]

Cancer*Care*
www.cancercare.org [28]

To find a genetic counselor in your area, ask your doctor or visit the following websites:

National Society of Genetic Counselors
www.nsgc.org [29]

National Cancer Institute: Cancer Genetics Services Directory
www.cancer.gov/cancertopics/genetics/directory

[30]

Links:
[1] http://www.cancer.net/cancer-types/hereditary-breast-and-ovarian-cancer
[2] http://www.cancer.net/node/18618
[3] http://www.cancer.net/node/19481
[4] http://www.cancer.net/node/19562
[5] http://www.cancer.net/node/19251
[6] http://www.cancer.net/node/19495
[7] http://www.cancer.net/node/18590
[8] http://www.cancer.net/node/18624
[9] http://www.uspreventiveservicestaskforce.org/uspstf/uspsbrgen.htm
[10] http://www.cancer.net/node/19645
[11] http://www.cancer.net/node/18783
[12] http://www.cancer.net/node/18505
[13] http://www.cancer.net/node/19133
[14] http://www.cancer.net/node/18715
[15] http://www.cancer.net/node/24714
[16] http://www.cancer.net/node/19565
[17] http://www.cancer.net/node/24959
[18] http://www.cancer.net/node/24868
[19] http://www.cancer.net/node/24895
[20] http://www.cancer.net/node/24907
[21] http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf
[22] http://www.facingourrisk.org/
[23] http://www.youngsurvival.org/
[24] http://www.ovarian.org/
[25] http://www.foundationforwomenscancer.org/
[26] http://www.cancer.gov/
[27] http://www.cancer.org/
[28] http://www.cancercare.org/
[29] http://www.nsgc.org/
[30] http://www.cancer.gov/cancertopics/genetics/directory