September is **Gynecologic Cancer Awareness Month**

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Facts About the Role of Heredity in Gynecologic Cancer

September is Gynecologic Cancer Awareness Month, established by the Foundation for Women's Cancer in 1999. Each year since, the Foundation has shared important facts with the public regarding gynecologic cancer risk, prevention, early detection and optimal post-diagnosis treatment during this special month.

This year's focus is on heredity and its role in gynecologic cancers. Considerable media attention has focused on BRCA1 and also BRCA2 genetic mutations because of Angelina Jolie Pitt's decisions to have both her breasts and ovaries removed to prevent breast and ovarian cancers in 2013 and 2015, respectively.

Camille Grammer, *Real Housewives of Beverly Hills* star and chair of the Foundation for Women's Cancer 2015 National Race to End Women's Cancer, speaks publicly about Lynch Syndrome, another cancer-causing genetic mutation, its role in her family's cancer history, and her own endometrial cancer survivorship journey.

What is a gene?

Genes are the building blocks of all cells that carry instructions for the body's functions. Inherited abnormalities in genes are called mutations and are present from birth in the genes of every cell in the body. They can be passed down from either parent and may, in turn, be passed on to children.

What are hereditary gynecologic cancer syndromes?

Cancers arise due to accumulation of damage to genes involved in controlling cell growth and DNA repair. In contrast to "sporadic" cancers, in which all mutations are acquired after birth, hereditary cancers arise in individuals who have inherited a mutation in a cancer-causing gene. These individuals generally develop cancer at a younger age than those with sporadic cancers and often develop multiple cancers.

Approximately 5 to 10% of cancers arise due to inherited mutations in genes responsible for hereditary cancer syndromes. The most common hereditary cancer syndromes that cause gynecologic cancers are hereditary breast-ovarian cancer syndrome and Lynch syndrome. Other inherited gene mutations may predispose women to gynecologic cancers to a lesser degree, but would not typically manifest as a hereditary cancer syndrome.

Hereditary Breast-Ovarian Cancer Syndrome

In the United States, approximately 10% of women will develop breast cancer and 1.5% will develop ovarian cancer. Inherited mutations in the BRCA1 and BRCA2 genes dramatically increase the risk of breast, ovarian, fallopian tube and peritoneal cancers. The lifetime risk of having one of the gynecologic cancers is 39-46% in BRCA1 carriers and 12-20% in BRCA2 carriers. These gene mutations also markedly increase breast cancer risk, causing a lifetime risk of 40-85% compared to 12% in the general population. Recently several other genes have been identified that increase ovarian cancer risk to about 5-15%, including BRIP1, RAD51C and RAD51D,

BRCA1 and BRCA2-associated cancers often occur at much earlier ages than most ovarian and breast cancers. It also is common to find multiple women with these cancers in affected families. Approximately one out of every 500 individuals in the general population has a mutation in one of the BRCA genes. In certain ethnic groups the mutation frequency is much higher. For example, one out of every 40 Ashkenazi Jewish individuals carry mutations. Both men and women can carry BRCA mutations and have a 50 percent chance of passing the mutation on to each of their children.

Lynch Syndrome

Lynch syndrome was named after Henry Lynch, who first described familial clustering of early onset colorectal cancer. This syndrome is due to inherited mutations in DNA mismatch repair genes, most often MSH2 and MLH1, but mutations may also occur in MSH6, PMS1 and PMS2. About one in 1000 individuals in the US carry a Lynch syndrome mutation. There is also an increased incidence of several other types of cancers in Lynch syndrome. Most notably, endometrial cancer risk is 40-60%.

About 3% of endometrial cancers are attributable to Lynch syndrome. The average age of diagnosis of endometrial cancer in Lynch syndrome is in the early 40s, compared to the early 60s for other cases. These cancers are usually confined to the uterus and are rarely fatal. The risk of ovarian cancer is also significantly increased to about 10%, but this accounts for only about 1% of all ovarian cancers. Ovarian cancers in women with Lynch syndrome also generally present at an early stage. The risk of stomach, small intestine, liver, brain and urinary system cancers is also increased.

The standard clinical criteria for diagnosis of Lynch syndrome include: (1) three or more relatives with Lynch syndrome-associated cancers; (2) two affected relatives in successive generations; (3) one affected relative is a first-degree relative of the other two, and; (4) one or more relatives with Lynch syndrome-associated cancer diagnosed before the age of 50.

If there is a concerning family history, genetic testing from a blood sample can be performed to detect the gene mutations that cause Lynch syndrome. In addition, screening for Lynch syndrome can be performed using cancer tissue by looking for loss of one of the mismatch repair genes or for a change know as microsatellite instability. Screening of all colorectal and endometrial cancers for Lynch syndrome has been advocated by some experts, but this practice has not been widely implemented. Another approach is to focus screening for Lynch syndrome on endometrial cancers with one or more of the following risk factors: family history of Lynch syndrome-associated cancers, young age of onset of endometrial cancer, lack of obesity (the main risk factor for endometrial cancer).

Women with Lynch syndrome should be monitored carefully by their healthcare provider. Current recommendations include frequent evaluation of the colon by colonoscopy starting in the 20's. Women should also be advised to consider having the CA125 blood test and transvaginal ultrasound annually to evaluate the ovaries, and a biopsy of the lining of the uterus (endometrium) annually beginning at age 25 to 35 years.

Colorectal cancer is the main cause of cancer mortality in Lynch syndrome. If a woman with Lynch syndrome requires surgical removal of the colon (colectomy) because of cancer or pre-cancer changes, it is also appropriate to remove the uterus and ovaries at the same time to reduce the risk of ovarian and endometrial cancer. Generally, this can be delayed until after childbearing is complete because Lynch syndrome-associated gynecologic cancers are infrequent prior to age 40 and are usually curable.

How do I know if I am at risk?

If you have a personal or family history of any of the following, you may be at risk for a hereditary cancer syndrome. Speak to your doctor, genetic counselor, or other qualified healthcare professional to determine if you

are at risk for Hereditary Breast and Ovarian Cancer Syndrome or Lynch syndrome. They will know best how to proceed with hereditary risk assessment and genetic testing if necessary.

Patients with an increased likelihood of having an inherited predisposition to breast and ovarian/tubal/peritoneal cancer who should be offered genetic testing.

Women AFFECTED with:

- Breast cancer before age 45.
- Breast cancer before age 50 and have at least one close relative who has had breast cancer prior to age 50, or ovarian cancer at any age, or a male relative with breast cancer at any age.
- Breast cancer before age 50 with a limited family history
- Breast cancer with ≥2 close relatives with breast cancer at any age
- Breast cancer with ≥2 close relatives with pancreatic cancer or aggressive prostate cancer (Gleason score ≥ 7)
- Two breast primary cancers, with the first diagnosed prior to age 50
- Triple negative breast cancer ≤60 years
- Breast cancer and Ashkenazi Jewish ancestry
- Pancreatic cancer with ≥2 close relatives with breast, ovarian/tubal/peritoneal, pancreatic, or aggressive prostate cancer (Gleason score ≥ 7)

Women UNAFFECTED with cancer, but with:

- A first degree or several close relatives that meet one of the above criteria
- A close relative carrying a known BRCA1 or BRCA2 mutation
- A close relative with male breast cancer.

As noted above, regardless of family history, genetic testing should be considered in women with high-grade ovarian, fallopian tube and peritoneal cancer, which comprises a majority of cases, as about 20% will be found to have BRCA mutations. Genetic testing is performed using a blood sample and generally begins by focusing on a family member who has been diagnosed with breast or ovarian cancer. If a mutation in either BRCA1 or BRCA2 is found, other family members can then be tested to see if they also inherited the same mutation.

For women who are at high risk on the basis of a strong family history or a positive BRCA gene test, a spectrum of options exist, including clinical monitoring (mammograms, CA125 blood test, pelvic ultrasound), preventive medications such as oral contraceptives and Tamoxifen, and prophylactic (preventive) surgery. Because of the lack of a reliable screening test for ovarian cancer, prophylactic removal of the ovaries and fallopian tubes is generally recommended after completion of childbearing, and also reduces breast cancer risk. The risk of uterine cancer is not increased, but hysterectomy is often performed as well, particularly if there is coexistent uterine pathology, such as fibroids or endometriosis.

How do I get tested?

A woman interested in undergoing genetic counseling and/or testing should speak to her healthcare provider to identify an appropriately trained individual who can provide these services.

Many healthcare providers can order genetic testing. However, not all providers have the experience needed to provide adequate counseling about who should be tested and which tests to order. Genetic counseling and testing can be conducted by genetic counselors as well as by other knowledgeable medical professionals.

Careful pre- and post-test counseling is essential to understanding genetic testing options and results. The increased complexity of testing options and results make detailed, individualized patient counseling by a knowledgeable provider an essential part of the testing process.

In the past, most genetic testing tested one gene at a time. Next generation sequencing is a new tool that allows inexpensive, rapid DNA sequencing. Current cancer gene panels vary in size from just 2 genes (i.e., BRCA1 and BRCA2) to larger panels that include more than 50 genes.

Cancer gene panel testing is increasingly being used because of the discovery of genes that increase cancer risk beyond BRCA1/2 and the Lynch syndrome genes. Other advantages of panel tests include decreased cost and improved efficiency of cancer genetic testing by reducing the time involved, number of patient visits, and number of tests sent. The major drawback of cancer gene panels is the increased complexity of the results. Panel tests increase the likelihood of finding alterations in the sequence of a gene for which the effect on cancer risk is uncertain. In addition, while we have clear guidelines for managing cancer risk in cases of BRCA1 and BRCA2 mutations and Lynch syndrome, for many other genes recommendations for mutation carriers are not established. Involving a cancer genetics professional is important to help order the most appropriate genetic test and to interpret the results.

IMPORTANT INFORMATION FOR WOMEN DIAGNOSED WITH EPITHELIAL OVARIAN, TUBAL AND PRIMARY PERITONEAL CANCERS

The Society of Gynecologic Oncology recommends that all women with high grade epithelial ovarian, tubal and primary peritoneal cancers should receive genetic counseling and be offered genetic testing, even in the absence of family history.

For ovarian cancer patients, knowing if you have BRCA1 or BRCA2 mutations may offer additional treatment options. On the basis of multiple trials, the FDA has given approval to the PARP inhibitor olaparib for use in women with inherited BRCA mutations who have received at least 3 lines of prior therapy. The response rate to olaparib in these patients is approximately 35%. This represents the first therapy approved for a specific population of ovarian cancer patients, officially welcoming the era of personalized therapy.

Other Resources Offered by the Foundation for Women's Cancer

Breast Cancer's Link to Ovarian Cancer: It's in Your Genes

Are You at Risk for Ovarian Cancer: A Woman's Guide

Understanding Your Risk for Ovarian Cancer: A Woman's Guide

If you suspect or have been diagnosed with a gynecologic cancer, seek care first from a gynecologic oncologist.

The Society of Gynecologic Oncology's (SGO) Foundation for Women's Cancer is dedicated to increasing public awareness of gynecologic cancer risk awareness, prevention, early detection and optimal treatment. Founded by SGO in 1991, the Foundation for Women's Cancer is a nonprofit organization that also provides funding for gynecologic cancer research and training, as well as educational programs and resources.