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Management and Patient Selection for BRCA Genetic Testing to Identify Women at Increased Risk for Breast and Ovarian Cancers: A Review

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Abstract: Cancer caused by a mutated gene is a hereditary cancer rather than a sporadic cancer. Women who have inherited mutations in the *BRCA1* or *BRCA2* genes have substantially elevated risks of breast and ovarian cancer. Further genetic risk assessment is recommended for women who have >20-25% chance of having an inherited predisposition to breast or ovarian cancer. Women with harmful mutations in either BRCA1 or BRCA2 have risk of breast cancer that is about 5 times the normal risk and a risk of ovarian cancer that is about 10-30 times normal. Mutation carriers have various options including extensive and regular surveillance, chemoprevention and risk-reducing surgery.

Key words: Brest cancer, *BRCA* gene mutation, surveillance, risk, women, Turkey

INTRODUCTION

Evaluating a patient's risk of hereditary breast and ovarian cancer syndrome is an important first step in cancer prevention and early detection and should be a routine part of obstetrics and gynecology practice. The American College of Obstetricians and Gynecologists (ACOG) and the Society of Gynecologic Oncologists (SGO) recommend routine assessment of a woman's risk of hereditary breast and ovarian cancer (ACOG, 2009).

Some families are at particularly high risk of cancer due to hereditary cancer syndromes. These families often have multiple family members with cancer and are more likely to develop cancer at a young age. In the case of breast and ovarian cancers, inherited mutations in two genes *BRCA1* and *BRCA2* have been found to greatly increase the lifetime risk of developing breast and ovarian cancer. These genes are involved in many vital cellular functions including DNA damage recognition, DNA repair and control of transcription (ACOG, 2009).

This study provides information on how to counsel patients with hereditary risk for cancer to prevent and how to perform surgical removal of the ovaries and fallopian tubes and breasts.

BRCA1 AND BRCA2 MUTATIONS

Approximately 10% of ovarian cancer cases and 3-5% of breast cancer cases can be traced to germ line mutations in the *BRCA1* and *BRCA2* genes (Risch *et al*., 2006). In the general population, about one in 300-800 persons carries a mutation in these genes (Whittemore *et al*., 1997).

Both men and women have *BRCA1* and *BRCA2* genes, so alterations and mutations in these genes can be passed down from either the mother or the father. The lifetime risk of a woman with a BRCA1 mutation has a 39-46% of developing ovarian cancer and a woman with a BRCA2 mutation has a 12-20% risk of developing ovarian cancer. The lifetime risk of breast cancer for a woman with a BRCA1 or BRCA2 mutation is 65-74% (Antoniou *et al*., 2003; King *et al*., 2003). In women with breast cancer, the 10 years risk of developing ovarian cancer is 12.7% for women with a BRCA1 mutation and 6.8% for women with a BRCA2 mutation (ACOG, 2009; Metcalfe *et al*., 2005).

Genetic testing is available to identify women at increased risk of breast and ovarian cancers. These women may benefit from screening and prevention strategies to reduce their risk.

RISK ASSESSMENT AND COUNSELING

The initial screening for hereditary breast and ovarian cancer syndrome should include specific questions about the patient's personal and family history of breast and ovarian cancers, risk assessment, education and counseling. The patient may choose to include genetic

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testing after appropriate counseling. Two sets of clinical criteria have been developed to determine which patients would benefit from genetic risk assessment. The first group includes women whose chance of having an inherited predisposition to breast and ovarian cancers is >20-25%. Genetic risk assessment is recommended in these patients. The second group includes women whose chance of having an inherited predisposition to breast and ovarian cancers is >5-10%. Genetic risk assessment may less be helpful for these patients. Patients who have been diagnosed with high-grade serous ovarian cancer, primary peritoneal cancer or fallopian tube cancer may also benefit from genetic risk assessment because of the high prevalence of BRCA1 or BRCA2 mutation in these populations (ACOG, 2009; Risch *et al*., 2006).

Further genetic risk assessment is recommended for women who have >20-25% chance of having an inherited predisposition to breast or ovarian cancer. These are:

- Women with a personal history of both breast cancer and ovarian cancer
- Women with ovarian cancer and a close relative-defined as mother, sister, daughter, grandmother, granddaughter, aunt-with ovarian cancer, premenopausal breast cancer or both
- Women with breast cancer at 50 or younger and who have a close relative with ovarian cancer or male breast cancer at any age
- Women with a close relative with a known BRCA mutation

As part of genetic counseling, physicians should discuss possible testing outcomes with patients including positive, negative and uninformative test results. Before testing, patients should be made aware of options for surveillance, chemoprevention and risk-reducing surgery (ACOG, 2009; Risch *et al*., 2006). It is also appropriate to discuss possible psychological and familial implications of testing as well as the expected costs and patients' insurance coverage. Another aspect of counseling may include a discussion of current legislation regarding genetic discrimination and the privacy of genetic information (ACOG, 2009). Genetic risk assessment may less be appropriate for women with 5-10% chance of having hereditary risk which are:

- Women with breast cancer by age 40
- Women with ovarian cancer, primary peritoneal cancer or fallopian tube cancer or high grade, serous histology at any age
- Women with cancer in both breasts (particularly if the first cancer was diagnosed by age 50)
- Women with breast cancer by age 50 and a close relative with breast cancer by age 50
- Women with breast cancer at any age and two or more close relatives with breast cancer at any age (particularly if at least one case of breast cancer was diagnosed by age 50)
- Unaffected women with a close relative that meets one of the previous criteria

GENETIC TESTING

Testing generally begins with a family member who has ovarian cancer or early-onset breast cancer. Full sequencing of BRCA1 and BRCA2 is often performed because the mutation may be found along the entire length of both genes. If a specific mutation is identified, a single-site test can be recommended to look for the specific mutation. In patients from high-risk ethnic and geographic groups where specific gene alterations are already identified, common mutations can be tested instead of full sequence testing (ACOG, 2009; Risch *et al*., 2006).

If no affected family member is available, patients may still benefit from testing. Counseling on screening or risk-reducing approaches is appropriate if a deleterious mutation is identified. If no deleterious mutation is identified, physicians should explain possible reasons for this such as a mutation that the patient did not inherit is present in the family; an undetectable mutation is present in the family but it is unknown whether the patient shares this predisposition or there is no inherited predisposition in the family. A physician with experience in caring for patients who may be at inherited risk can determine which option is most likely and which risk-reduction approach is appropriate for the patient (ACOG, 2009; Risch *et al*., 2006). As a result, patients identified as having >20-25% risk of having a BRCA mutation (high risk) who are referred for genetic counseling.

RISK-REDUCTION STRATEGIES

Ovarian and fallopian tube cancers: Strategies to reduce the risk of ovarian and fallopian tube cancers in women with known BRCA mutations include surveillance, chemoprevention and surgery. Current screening procedures are not likely to detect ovarian cancer at an early enough stage to cure the disease. Patients should be informed that there is no evidence that screening will reduce mortality from ovarian cancer in high-risk populations. However because of the high risk of ovarian and fallopian tube cancers in women with BRCA1 or BRCA2 mutations, periodic screening with cancer antigen

Ca-125 and transvaginal ultrasonography are appropriate. Screening should begin between 30 and 35 years of age or 5-10 years earlier than the earliest age of first diagnosis of ovarian cancer in the patient's family (Burke *et al*., 1997; NCCN, 2009).

Athough, studies have reported the benefits and magnitude of reduced risk of ovarian cancer with oral contraceptive use in women with a BRCA mutation (Modan *et al*., 2001), this has not been demonstrated consistently in the general low-risk population. Some studies have suggested that oral contraceptive use increases the risk of breast cancer in women with BRCA mutations (Modan *et al*., 2001). Physicians should discuss the risks and benefits of chemoprevention and oral contraceptives with patients who have BRCA1 or BRCA2 mutations. Parity has been associated with a lower risk of ovarian cancer in women with a BRCA mutation (ACOG, 2009; Modan *et al*., 2001; Brohet *et al*., 2007).

Risk-reducing salpingo-oophorectomy of normal ovaries and fallopian tubes should be offered to women by 40 years of age or after childbearing. This procedure has been shown to reduce the risk of ovarian, fallopian tube and peritoneal cancers by 85-90% as well as decrease overall mortality in women with a BRCA mutation (Finch *et al*., 2006).

Breast cancer: Strategies to reduce the risk of breast cancer in women with known deleterious BRCA mutations include surveillance, chemoprevention and surgery. Surveillance methods include semiannual clinical breast examination, annual mammography and annual breast magnetic resonance imaging beginning at 25 years of age or earlier based on the earliest age of onset in the patient's family (NCCN, 2009).

Preliminary studies suggest that chemoprevention with tamoxifen may reduce the risk of breast cancer by 62% in women with BRCA2 mutations although, it does not reduce the risk in women with BRCA1 mutations (King *et al*., 2001). Prophylactic surgery with bilateral mastectomy has been shown to reduce the risk of breast cancer by >90-95% depending on the type of mastectomy procedure. The most effective procedure is total mastectomy which removes the entire breast tissue, nipple and areola (Dowdy *et al*., 2004).

Risk-reducing salpingo-oophorectomy has demonstrated a reduction in the risk of breast cancer by 40-70%. This protection is likely limited to patients who are premenopausal at the time of surgery (Kauff *et al*., 2008). Carriers of the BRCA2 mutation may experience a greater protective effect than carriers of the BRCA1 mutation. The timing of risk-reducing salpingo-oophorectomy should be based on the patient's needs such as the desire to preserve fertility and which gene mutation the patient carries (ACOG, 2009).

MANAGEMENT FOR WOMEN WITHOUT IDENTIFIED BRCA MUTATIONS

Current testing methods cannot identify all mutations that exist in *BRCA* genes (Walsh *et al*., 2006). Studies suggest that breast cancer is caused by a BRCA mutation in less than one half of families with four or more cases of breast cancer but no cases of ovarian cancer (Rodriquez and Domchek, 2007). Women with a personal or family history of breast cancer who test negative for a BRCA mutation should be treated based on their family history (ACOG, 2009). There is an increased risk of breast cancer in women with a family history of site-specific breast cancer who have no identified BRCA mutation. However, these women may not have an increased risk of ovarian cancer (Kauff *et al*., 2005). Women at high risk of breast and ovarian cancers should maintain contact with their physician to keep informed of new research and improvements in testing technology (ACOG, 2009).

CONCLUSION

A genetic risk assessment is recommended for patients with a >20-25% chance of having an inherited predisposition to breast and ovarian cancer. When women are referred for additional genetic risk assessment, this often includes the collection of additional family history information, education and counseling (ACOG, 2009). Genetic testing may also be conducted. If a woman undergoes genetic testing and tests positive for a BRCA1 or BRCA2 mutation, she has several options for managing her risk of breast and ovarian cancer such as surveillance, chemoprevention and prophylactic (preventive) surgery. Surveillance, women may choose to undergo regular cancer screening in order to detect cancer at an early stage. This screening may need to begin at an early age. Screening tests for breast and ovarian cancer include clinical breast exam, mammography, breast Magnetic Resonance Imaging (MRI), CA 125 testing and transvaginal ultrasonography. It's important for women to be aware that there is still no clear evidence that screening for ovarian cancer reduces the risk of death from the disease. Chemoprevention hormonal therapy with tamoxifen has been shown to reduce the risk of breast cancer among women with a BRCA2 mutation. Tamoxifen may provide less of a breast cancer benefit among women with a BRCA1 mutation. Prophylactic (preventive)

surgery; bilateral prophylactic mastectomy (surgical removal of both breasts before cancer develops) greatly reduces the risk of breast cancer in women with a BRCA1 or BRCA2 mutation. Similarly, prophylactic removal of the ovaries and fallopian tubes reduces the risk of ovarian, fallopian tube and peritoneal cancer. For women who are premenopausal, removal of the ovaries also reduces the risk of breast cancer.

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