Breast and Ovarian Cancer: Known ***BRCA1*** Mutation in the Family

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Key Points

- Relatives of a person with a known *BRCA1* or *BRCA2* mutation can be offered testing to determine whether they have inherited the mutation.
- Considerations in the testing decision include medical management, personal preferences, and family issues.

Learning Objectives

Participants will be able to:

- Describe the testing options for a close relative of a person with a known *BRCA1* or *BRCA2* mutation;
- Describe the issues to be reviewed with the patient who is considering testing.

Family History Issues

When testing identifies a person with a *BRCA1* or *BRCA2* mutation, it also infers that other family members are at risk of having the same mutation. The likelihood that a relative has the mutation is based on the rules of autosomal dominant inheritance.

First-degree relatives have a 50% risk of having inherited the mutation; for their offspring, the risk of inheriting the mutation is 25%. Further testing can identify additional relatives at risk or, in the case of negative result, can identify relatives who are no longer at risk. For example, if a woman has a *BRCA1* mutation, and her sister tests negative for the mutation, her sister's children cannot inherit it.

Testing allows family members to determine whether they have inherited a cancer predisposition; information from test results can help family members to plan appropriate preventive care.

Red Flags 

Some clinical presentations raise the question of inherited breast/ovarian cancer:

- Breast cancer occurring at a young age — for example, breast cancer before age 45
- Two or more cancers in a single individual — for example, bilateral or multifocal primary breast cancer, or breast and ovarian cancer
- Breast cancer in a male

If a patient has any of these clinical presentations, s/he may have affected relatives who have already undergone *BRCA1* and/or *BRCA2* testing. If so, obtaining the relatives' test results will be useful in determining the testing options for the patient.

Case 3. College Student Asks about the Breast Cancer Genetic Test Her Mother Had

A 20-year-old college student comes in during her winter vacation, at the urging of her father. Her mother was diagnosed with breast cancer a year ago, at age 43. Metastases were already present at the time of the diagnosis, and her mother died in August. Testing done a few weeks before her mother's death revealed a mutation in the *BRCA1* gene. The patient has come in because her father says she ought to be tested. She brings a copy of her mother's *BRCA1* test result.

Clinical Care Issues

The patient may have inherited a cancer-predisposing *BRCA1* mutation from her mother. If so, she would have a high lifetime risk for breast and ovarian cancer, and would be a candidate for specific screening tests and other preventive care to reduce her risk. Current recommendations for women with *BRCA1* and *BRCA2* mutations include the initiation of breast screening at age 25-30. No earlier interventions are recommended [Burke et al 1997, NCCN Guidelines].

Risk Assessment

This patient has a 50% risk of having inherited the *BRCA1* mutation found in her mother. If she inherited the mutation, she has a high lifetime risk for breast cancer (estimated at 50% to 85%) and of ovarian cancer (estimated at 40%). If she did not inherit the mutation, her risks are probably at or close to baseline population risk.

Genetic Counseling and Testing

The first step in counseling this patient would be to assess her concerns and questions. It is not clear whether she is interested in genetic testing, or has simply come in at her father's suggestion. It is likely that she is still grieving the death of her mother, and may have considerable anxiety about the implications of her mother's cancer for herself.

The patient has a 50% risk of having inherited the *BRCA1* mutation from her mother. She will benefit from an understanding of the genetics of breast ovarian cancer syndrome, and from the opportunity to consider the implications of positive and negative genetic test results.

A positive test result would confirm that she has a high risk for both breast and ovarian cancer. However, no risk-reducing measures would be recommended until she is at least 25. Thus, she does not need to rush a testing decision. She may prefer merely to gather information and consider her options. Preparing for testing, and the possibility of a positive test result, may be easier when she has had more time to adjust to her mother's death. She should be given information about the preventive measures offered to women with *BRCA1* mutations (see Interventions), with the clear understanding that no specific preventive care is needed immediately.

The patient may have questions about her mother's cancer course, which was unusually rapid and therefore likely to have been tragic for the family. She may worry that if she develops cancer her own course will be similar. However, her mother's course was atypical. It is not clear whether women with *BRCA1* mutations generally have a more severe course than other women their age with breast cancer. Some studies have suggested poorer prognosis [Johannsson et al 1998, Stoppa-Lyonnet 2000] while others have not [Chabner et al 1998, Verhoog et al 1998]. It is known, however, that women with *BRCA1* and *BRCA2* mutations have a much higher rate of contralateral breast cancer than other breast cancer patients [Verhoog et al

1998, Haffty et al 2002], as well as high lifetime risk for ovarian cancer. Nevertheless, cancer course is variable among women with *BRCA1* and *BRCA2* mutations, as it is among other women with breast cancer, and some women experience long-term survival after treatment.

Interventions

Several interventions are recommended for women who have a *BRCA1* or *BRCA2* mutation. These interventions are supported by expert opinion and retrospective and prospective observational data, including both cohort and case-control studies. A detailed review of the evidence related to these interventions can be found in the National Cancer Institute PDQ review: Genetics of Breast and Ovarian Cancer. These interventions include:

- **Breast cancer screening.** Mammography screening has not been extensively evaluated in high-risk women; prospective studies of MRI screening suggest that it has higher sensitivity than mammography but may occasionally miss cancers seen on mammography. Most experts recommend that screening be initiated by age 30, and that mammography and MRI screening be used alternately on a six-monthly basis.
- **Ovarian cancer screening.** Methods for screening include vaginal ultrasound and measurement of serum CA-125 level. These strategies have limited sensitivity and specificity, and are of uncertain benefit.
- **Tamoxifen.** A US randomized trial demonstrated reduction in breast cancer occurrence over four years of treatment among women with increased risk as estimated by the Gail statistical model [Gail et al 1989]. A subset analysis suggested that women with a *BRCA2* mutation may benefit from this treatment, but women with a *BRCA1* mutation may not.
- **Risk-reducing mastectomy.** Both retrospective and prospective observational studies indicated that breast cancer risk is substantially reduced (>90%) by this surgery. Observational studies suggest that only a minority of women elect to have this surgery prior to a cancer diagnosis.
- **Risk-reducing oophorectomy.** Both retrospective and prospective observational studies indicate that ovarian cancer risk is substantially reduced (>90%) by this surgery.

Ethical/Legal/Social/Cultural Issues

Careful counseling should be provided prior to testing for inherited cancer

susceptibility [Biesecker et al 1993, Geller et al 1997]. Knowledge of an inherited predisposition may cause anxiety and family distress, and may also pose other risks, such as loss of insurance or employment opportunities. For this patient, testing may feel particularly threatening because of the recent loss of her mother.

Tensions may occur between family members related to inherited risk. For example, the patient's father may see testing as a protective measure for his daughter, and for this reason may be urging her to proceed. However, she may not yet be ready to consider her personal risks and the decisions she will ultimately face concerning preventive measures such as prophylactic surgery. As a result, she may experience her father's urging as coercive. In the initial stages of counseling, it may be more important to ensure that the patient has adequate emotional support, and is able to discuss her fears in a supportive environment, than to address specific medical issues.

Resources

- **American Cancer Society**
  Provides contact information for regional support groups and programs, cancer information, patient and family education materials, and free mammograms.
  1599 Clifton Rd NE
  Atlanta, GA 30329
  Phone: 800-227-2345

- **Breast Cancer Information Core** **NHGRI (National Human Genome Research Institute) Cancer Genetics Branch**
  Breast cancer resources on the Web

- **NCI (National Cancer Institute) Breast Cancer Home Page**

- **CancerCare**
  275 7th Avenue
  New York, NY 10001
  Phone: 212-712-8080; 1-800-813-HOPE (4673)
  Fax: 212-712-8495
  Email: info@cancercare.org

- **Facing Our Risk of Cancer Empowered (FORCE)**
  A discussion forum specifically for women who are at a high risk of developing ovarian cancer or breast cancer.
  934 N University Dr, PMB #213
  Coral Springs, FL 33071
  Phone: 954-255-8732
  Email: info@facingourrisk.org

- **Genetics of Breast and Ovarian Cancer (PDQ)**
  A service of the National Cancer Institute

- **Gilda's Club**
  322 Eighth Avenue, Suite 1402
  New York, NY 10001
  Phone: 1-888-GILDA-4-U
  Fax: 914-304-0549
  Email: info@gildasclub.org

- **Mid-Atlantic Cancer Genetics Network: Breast / Ovarian Cancer**

- **The National Alliance of Breast Cancer Organizations**
  An advocacy group that serves as an umbrella for 370 breast cancer groups nationwide. Provides information, a newsletter, and treatment information. Also provides grants for programs on early detection and education.
  9 East 37th Street, 10th Floor
  New York, NY 10016
  Phone: 212-889-0606; 888-806-2226
  Fax: 212-689-1213
  Email: NABCOinfo@aol.com

- **National Breast Cancer Centre Home Page-Australia**

- **The National Breast Cancer Coalition**
  An advocacy group seeking public policy change to benefit breast cancer patients and survivors
  1701 L St NW, Suite 1060
  Washington DC 20036
  Phone: 202-296-7477; 800-935-0434

- **NCBI Genes and Disease Webpage: Breast cancer**

- **National Cancer Institute**

- **The National Coalition for Cancer Survivorship**
  A consumer organization that advocates on behalf of all people with cancer
  1010 Wayne Avenue, Suite 770
  Silver Spring, MD 20910
  Phone: 877-NCCS-YES (877-622-7937)
  Fax: 301-565-9670
  Email: info@cansearch.org

- **National Library of Medicine Genetics Home Reference: Breast cancer**

- **Ovarian Cancer (National Ovarian Cancer Coalition)**
  500 NE Spanish River Blvd, Suite 14
  Boca Raton, FL 33431
  Phone: 1-888-OVARIAN; 561-393-0005
  Fax: 561-393-7275
  Email: nocc@ovarian.org

- **Susan G Komen Breast Cancer Foundation**
  Information, referrals to treatment centers. Answers questions from recently diagnosed women and provides emotional support. Funds research and programs for women who do not have adequate medical service and support.
  Occidental Tower
  5005 LBJ Freeway, Suite 370 LB74
  Dallas, TX 75244
  Phone: 800-462-9273 (hotline); 214-450-1777
  Email: helpline@komen.org

- **US Preventive Services Task Force Guidelines on Genetic Risk Assessment and *BRCA* Mutation Testing for Breast and Ovarian Cancer Susceptibility**

- **Y-Me National Organization for Breast Cancer Information**
  Hotline staffed by counselors and volunteers who have had breast cancer. Information, referrals, support.
  212 West Van Buren St, Suite 500

Chicago IL 60607
Phone: 800-221-2141
Fax: 312-294-8597

- **Cancernet: PDQ® Cancer Information Summaries: Genetics**
- **GeneTests Online Medical Genetics Information Resource**
- ***GeneReview:* BRCA1/BRCA2 Hereditary Breast/Ovarian Cancer**
- **GeneTests Resources for Breast and Ovarian Cancer**

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