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Breast and Ovarian Cancer: An Important Public Health Problem

Breast cancer is the most common form of cancer in United States women (approximately 216,000 new cases will be diagnosed in 2004), and the second most common cause of cancer deaths (approximately 40,000 deaths per year).[1] Ovarian cancer is less common (about 25,000 new cases each year), but about three-quarters of cases are diagnosed at a late stage, when it is often fatal. Each year, an estimated 809,000 person-years of life are lost due to breast cancer, and 232,000 person-years are lost due to ovarian cancer.[2]

Genetic Tests for Breast and Ovarian Cancer Susceptibility

Most breast and ovarian cancers occur after menopause, and the risk increases with age. Because most symptoms and clinical signs of breast cancer are relatively specific and well understood, an early diagnosis is possible through established mammography screening programs. Ovarian cancer signs and symptoms are not apparent in the early stages and routine screening is not recommended for the general population. Diagnosis of breast or ovarian cancer is by biopsy and pathologic examination.

Two genes, *BRCA1* and *BRCA2* (*BR*east *CA*ncer genes), are associated with predisposition to hereditary breast or ovarian cancer. Mutations in these genes are identified in 1-2% of women with breast cancer and 5-10% of women with ovarian cancer.[3] A prominent characteristic of these inherited cancers is early age at onset. Women identified with a *BRCA1* or *BRCA2* mutation have a substantially increased risk of developing breast and/or ovarian cancer during their lifetime. These risks are compared with those in the general population in the following table:

Table 1. Risks of Developing Breast and Ovarian Cancer by Age 70 in the General Population Compared with Women with a *BRCA1* or *BRCA2* Mutation

Cancer Type	General Population Risk By Age 70[4] (%)	*BRCA1* or *BRCA2* Mutation Risk By Age 70[3](%)
Breast Cancer	9.7	35 – 85
Ovarian Cancer	~ 1	9 – 66

The two *BRCA* genes have been patented. As a result, one laboratory performs most clinical testing for *BRCA* mutations in the U.S. and the test itself is trademarked under the name BRACAnalysis™. Comprehensive *BRCA* analysis is one form of the test that examines the full sequence of the *BRCA1* and *BRCA2* genes to look for mutations that indicate a predisposition to hereditary breast and ovarian cancer.

A Public Health Perspective

Genetic testing for *BRCA1* and *BRCA2* mutations is a complex process and is not recommended for women in the general population. At present, *BRCA1* and *BRCA2* mutation testing may be appropriate for only a small proportion of women (less than one percent). These women can make an informed decision about testing in collaboration with their health care providers. An informed decision requires that the potential benefits and potential risks or limitations of testing are considered.

The Role of Family History in *BRCA1* and *BRCA2* Testing

The first step in considering *BRCA1* and *BRCA2* mutation testing for adult women is to ask about the woman's family history of breast and ovarian cancer because:

- most breast and ovarian cancers are not inherited, but occur sporadically;
- *BRCA1* and *BRCA2* mutations are uncommon (about 1 in 400 women carry a mutation);
- the cost of full genetic testing (Comprehensive BRACAnalysis) is nearly $3000;
- women with a strong family history are more likely to have a mutation.

Screening women by asking their family history is relatively inexpensive and identifies families in which the chance of finding a *BRCA1* or *BRCA2* mutation is at least 10%. It does, however, have disadvantages:

- there is no standard definition of a positive family history for breast/ovarian cancer;
- about half of the women who carry a *BRCA1* or *BRCA2* mutation will not have a positive family history;[3]
- in most families with a positive history of breast and ovarian cancer, *BRCA1* and *BRCA2* mutations are not involved;[3,5]
- some types of mutations in the *BRCA1* or *BRCA2* genes are not detectable by the methodology used for Comprehensive BRACAnalysis.

The Role of Genetic Counseling in *BRCA1* and *BRCA2* Testing

Organizations commonly recommend that when a woman considering *BRCA1* and *BRCA2* mutation testing has a family history suggestive of inherited breast and ovarian cancer, she should consult with a genetic counselor or other provider with experience in cancer genetics.[6,7] The decision to undergo genetic testing is complicated and involves understanding the nature and risks of breast and ovarian cancers and the risks, benefits and alternatives to genetic testing. Women will need to consider these issues along with their preferences and values.[8]

The process of genetic counseling is designed to assist in:

- understanding the test and its limitations,
- understanding medical facts,
- understanding the hereditary contribution to the disorder, and
- choosing the course of action that is appropriate, based on level of risk, family goals, and ethical and religious beliefs.

Resources are available to assist health care providers and patients in locating genetic counseling services in their area (e.g., http://www.nsgc.org).

BRCA1 and *BRCA2* Mutation Testing

If the woman seeking genetic testing has not had breast or ovarian cancer, organizations that support genetic testing recommend that a family member with cancer be tested first.[6] If a mutation is not found, testing of other family members is not warranted. If a mutation is detected, subsequent testing of family members is simpler (and cheaper) because testing is focused on the identified mutation.

Family members found to have the identified mutation are at increased risk for developing breast or ovarian cancer. Family members who do not have the identified mutation have the same risk for developing breast or ovarian cancer as members of the general population with similar demographic and environmental characteristics.

If mutation testing cannot be performed on an affected family member, further genetic testing of family members may not be warranted because the test results might not be informative. For example, finding no mutations in a woman who does not have cancer does not distinguish between the possibilities that:

1. she did not inherit a *BRCA1* or *BRCA2* mutation that caused cancer in other family members, or

2. the increased risk of cancer in her family is not caused by a detectable *BRCA1* or *BRCA2* mutation.

If a woman is found to have *BRCA1* or *BRCA2* mutation, she may benefit because she knows she is at higher risk and she may choose some medical options discussed in the following section. Finding a mutation prompts several additional considerations:

- Carrying a mutation may present psychological and social dilemmas, and introduce the potential for employment and/or insurance discrimination.

- Males can also carry a *BRCA*1 or *BRCA*2 mutation. In males, mutations in *BRCA*1 and *BRCA*2 have been associated with an increased risk of male breast cancer (especially *BRCA*2 mutations) and prostate cancer.

- Approximately 13% of Comprehensive BRACAnalysis tests report a variant of "uncertain clinical significance".[9] This means that it is unknown whether or not these variants are associated with increased cancer risk, so that the woman will not know if her test result signifies an increased risk of cancer.

Surveillance and Risk-Reducing Strategies for Breast and Ovarian Cancer

Organizations that recommend testing and genetic counseling also recommend surveillance for women who choose not to have risk reducing surgeries.

Breast Cancer Surveillance by Mammography and/or Magnetic Resonance Imaging (MRI):

- Increased surveillance for early breast cancer detection is acceptable to at least half of women with a *BRCA1* or *BRCA2* mutation.[3]

- In women with *BRCA1* or *BRCA2* mutations, surveillance will identify about two-thirds of the breast cancers.[3]

- How effective breast cancer surveillance is in reducing mortality in women with a *BRCA1* or *BRCA2* mutation is not known.

- The false positive rate of breast cancer surveillance in women with a BRCA1 or *BRCA2* mutation is not known.

Ovarian Cancer Surveillance by Serum Tumor Markers and/or Ultrasonography:

- Increased surveillance for ovarian cancer detection is less acceptable than breast cancer surveillance in women with a *BRCA1* or *BRCA2* mutation.[3] This is likely because the effectiveness of these tests in detecting cancer and reducing mortality is uncertain.[3]

- About 4% of women who undergo surveillance for ovarian cancer will have a false positive result—that is, they will also have exploratory surgery that does not detect ovarian cancer.[3]

Risk-Reducing Surgeries

Risk-reducing surgeries are the most effective means of preventing breast and/or ovarian cancer. While women with *BRCA1*or *BRCA2* mutations who choose preventive mastectomy (surgical removal of breast tissue) may reduce their risk of breast cancer by at least 90%, acceptance of this option is 15% or less in the U.S.[3] Oophorectomy (surgical removal of the ovaries) may reduce the risk of breast cancer by about half and the risk of ovarian cancer by nearly 100%.[3] Oophorectomy has higher acceptance (13-50%, depending on the study) among BRCA mutation carriers, particularly those over age 40 (64-78%).[3]

Chemoprevention

Chemoprevention of breast cancer is another option, but is less acceptable to women regardless of mutation status, possibly due to side effects such as blood clots.[10] In one study, only 5% of all women accepted treatment by tamoxifen.[11] There is also some uncertainty about the effectiveness of tamoxifen in reducing the risk of breast cancer in women who carry *BRCA1* or *BRCA2* mutations.[12,13]

Lifestyle Changes

Although excess body weight and physical inactivity may be responsible for about one fourth to one third of breast cancers in women in the general population,[14] the effects of lifestyle modifications (e.g., diet, exercise, not smoking) in *BRCA1* and *BRCA2* mutation-positive women have not been directly studied. Patients at increased risk may welcome the opportunity to be in control of these aspects of their lives and may enjoy improved health.

Evaluation of *BRCA1* and *BRCA2* Testing in Practice

Although at least four organizations have issued guidelines on the use of *BRCA1* and *BRCA2* mutation testing for breast and ovarian cancer susceptibility in the U.S.,[3] no one set of guidelines has been universally accepted and implemented in clinical practice. This is due in part to the small amount of information available to assess how well the test identifies women who may benefit from testing and how effective and acceptable the interventions are. Other reasons may include the complexity of implementing and interpreting family history questionnaires. See *Chapter 10, Ensuring the Quality of Genetic Testing in the United States*, for more information.

Understanding the public health impact of genetic tests also requires the collection of data to investigate performance in practice, as well as quality, utilization and access. Collaboration between public health agencies, clinical care providers, professional organizations, and industry will be needed to collect this information. Related projects supported by CDC include:

- an evidence-based ACCE Review on *BRCA1* and *BRCA2* mutation testing in women with a family history of breast/ovarian cancer (ACCE is a model process for evaluating data on genetic tests; see http://www.cdc.gov/genomics/activities/fbr.htm),

- a study by the U.S. Preventive Services Task Force to examine the clinical utility of *BRCA1* and *BRCA2* mutation testing, funded by the Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, CDC, and

- a study to determine the impact on knowledge, attitudes and actions of a direct-to-consumer advertising campaign about *BRCA1* and *BRCA2* mutation testing that targeted women and their health care providers in two pilot cities, Atlanta, GA and Denver, CO.

Effectiveness of *BRCA1* and *BRCA2* Testing for Prevention

- Overall, *BRCA1* and *BRCA2* mutations are responsible for only a few percent of breast and ovarian cancers, but effective risk-reducing strategies are available.

- Access to these risk-reducing strategies may be limited by lack of insurance or inadequate coverage, failure of health care providers to appropriately refer, or availability of services in certain areas.

- Limited information is available about implementation issues surrounding the use of a routine family history plus *BRCA1* and *BRCA2* mutation testing strategy. Limited information is also available about the economic consequences.

- Acceptance of mutation testing is also limited by other issues, such as adverse health consequences of some prevention strategies and social stigmatization.

Conclusion

Genetic testing for *BRCA1* and *BRCA2* mutations may be appropriate for individuals with specific family histories of breast and/or ovarian cancer. There are many issues that must be considered throughout the testing process in order for an individual to make an informed decision regarding testing.

References

1. American Cancer Society. Cancer Facts and Figures. Web site. Available at: http://www.cancer.org/downloads/MED/Page4.pdf. Accessed Mar 29, 2004.
2. Brown ML, Lipscomb J, and Snyder C. The burden of illness of cancer: economic cost and quality of life. *Annu Rev Public Health* 2001; 22:91-113.
3. McClain MR, Palomaki GE, Haddow JE. Breast and ovarian cancer. *ACCE Review*. Web site. Available at: http://www.cdc.gov/genomics/activities/fbr.htm. Accessed Mar 31, 2004.
4. Feuer EJ, Wun LM. DEVCAN: Probability of Developing or Dying of Cancer Software [computer program]. Version 5.0. Bethesda (MD): National Cancer Institute; 1999.
5. Pinsky LE. Why should primary care physicians know about breast cancer genetics? *West J Med* 2001;175:168-73.
6. New York State Dept. of Health and American College of Medical Genetics. Genetic susceptibility to breast and ovarian cancer: assessment, counseling and testing guidelines. 1999. Web site. Available at: http://www.health.state.ny.us/nysdoh/cancer/obcancer/contents.htm. Accessed Mar 30, 2004.
7. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. *J Clin Oncol* 2003;21:2307-406.
8. Sheridan SL, Harris RP, Woolf SH, for the Shared Decisionmaking Workgroup. Shared decisionmaking about screening and chemoprevention: a suggested approach from the U.S. Preventive Services Task Force. Article originally in *Am J Prev Med* 2004;26(1): 56-66. Agency for Healthcare Research and Quality, Rockville, MD. Also available at: http://www.ahrq.gov/clinic/3rduspstf/shared/sharedba.htm. Accessed Mar 30, 2004.
9. Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. *J Clin Oncol* 2002; 20:1480-90.
10. U.S. Preventive Services Task Force. Chemoprevention of breast cancer: recommendations and rationale. July 2002. Agency for Healthcare Research and Quality, Rockville, MD. Web site. Available at http://www.ahrq.gov/clinic/3rduspstf/breastchemo/breastchemorr.htm. Accessed Mar 30, 2004.

11. Port ER, Montgomery LL, Heerdt AS, and Borgen PI. Patient reluctance toward tamoxifen use for breast cancer primary prevention. *Ann Surg Oncol*. 2001; 8:580-5.

12. Narod SA, Brunet JS, Ghadirian P, Robson M, Heimdal K, Neuhausen SL, et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Hereditary Breast Cancer Clinical Study Group. *Lancet* 2000;356:1876-81.

13. King MC, Wieand S, Hale K, Lee M, Walsh T, Owens K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. *JAMA* 2001;286:2251-6.

14. International Agency for Research on Cancer. Weight control and physical activity. IARC Handbooks of Cancer Prevention, Vol. 6. IARC Press, Lyon, 2002.