U.S. Preventive Services Task Force

Risk Assessment, Genetic Counseling, and Genetic Testing for *BRCA*-Related Cancer in Women: Recommendation Statement

▶ **See related Putting Prevention into Practice on page 119.**

This summary is one in a series excerpted from the Recommendation Statements released by the USPSTF. These statements address preventive health services for use in primary care clinical settings, including screening tests, counseling, and preventive medications.

The complete version of this statement, including supporting scientific evidence, evidence tables, grading system, members of the USPSTF at the time this recommendation was finalized, and references, is available on the USPSTF website at http://www.uspreventiveservicestaskforce.org/.

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A collection of USPSTF recommendation statements published in *AFP* is available at http://www.aafp.org/afp/uspstf.

Summary of Recommendations and Evidence

The U.S. Preventive Services Task Force (USPSTF) recommends that primary care clinicians screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with one of several screening tools designed to identify a family history that may be associated with an increased risk of potentially harmful mutations in breast cancer susceptibility genes (*BRCA1* or *BRCA2*). Women with positive screening results should receive genetic counseling and, if indicated after counseling, *BRCA* testing. **B recommendation.**

The USPSTF recommends against routine genetic counseling or *BRCA* testing for women whose family history is not associated with an increased risk of potentially harmful mutations in the *BRCA1* or *BRCA2* gene. **D recommendation.**

Rationale

IMPORTANCE

The cancer types related to potentially harmful mutations of the *BRCA* genes are predominantly breast, ovarian, and fallopian tube cancer, although other types are also associated.[1] In the general population, 12.3% of women will develop breast cancer during their lifetime and 2.7% will die of the disease, whereas 1.4% of women will develop ovarian cancer and 1.0% will die of the disease.[2] A woman's risk of breast cancer increases to 45% to 65% by 70 years of age if there are clinically significant mutations in either *BRCA* gene.[3,4] Mutations in the *BRCA1* gene increase ovarian cancer risk to 39% by 70 years of age, and *BRCA2* mutations increase ovarian cancer risk to 10% to 17% by 70 years of age.[3,4] In the general population, these mutations occur in an estimated one in 300 to 500 women (0.2% to 0.3%).[5-8] In a meta-analysis conducted for the USPSTF, the combined prevalence of *BRCA1* and *BRCA2* mutations was 2.1% in a general population of Ashkenazi Jewish women.[9]

DETECTION OF POTENTIALLY HARMFUL *BRCA* MUTATIONS

Genetic risk assessment and *BRCA* mutation testing is generally a multistep process involving identification of individuals who may be at increased risk of potentially harmful mutations, followed by genetic counseling from suitably trained health care professionals and genetic testing of selected high-risk individuals when indicated. Several familial risk stratification tools are clinically useful for selecting patients who should be offered genetic counseling to further determine their candidacy for possible *BRCA* mutation testing.

BENEFITS OF TESTING FOR POTENTIALLY HARMFUL *BRCA* MUTATIONS

For women whose family history is associated with an increased risk of potentially harmful mutations in the *BRCA1* or *BRCA2* gene, adequate evidence suggests that the benefits of testing for potentially harmful *BRCA* mutations are moderate.

For women whose family history is not associated with an increased risk of potentially harmful mutations in the *BRCA1* or *BRCA2* gene, there is adequate evidence that the benefits of testing for potentially harmful *BRCA* mutations are few to none.

HARMS OF DETECTION OF POTENTIALLY HARMFUL *BRCA* MUTATIONS AND EARLY INTERVENTION AND TREATMENT

Adequate evidence suggests that the overall harms of detection of and early intervention

Table 1. Risk Assessment, Genetic Counseling, and Genetic Testing for *BRCA*-Related Cancer in Women: Clinical Summary of the USPSTF Recommendation

Population	Asymptomatic women who have not been diagnosed with *BRCA*-related cancer	
Recommendation	Screen women whose family history may be associated with an increased risk of potentially harmful *BRCA* mutations. Women with positive screening results should receive genetic counseling and, if indicated after counseling, *BRCA* testing. Grade: B	Do not routinely recommend genetic counseling or *BRCA* testing to women whose family history is not associated with an increased risk of potentially harmful *BRCA* mutations. Grade: D
Risk assessment	Family history factors associated with increased likelihood of potentially harmful *BRCA* mutations include breast cancer diagnosis before 50 years of age, bilateral breast cancer, family history of breast and ovarian cancer, presence of breast cancer in one or more male family members, multiple cases of breast cancer in the family, one or more family members with two primary types of *BRCA*-related cancer, and Ashkenazi Jewish ethnicity. Several familial risk stratification tools are available to determine the need for in-depth genetic counseling, such as the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, and FHS-7.	
Screening tests	Genetic risk assessment and *BRCA* mutation testing are generally multistep processes involving identification of women who may be at increased risk of potentially harmful mutations, followed by genetic counseling by suitably trained health care professionals and genetic testing of selected high-risk women when indicated. Tests for *BRCA* mutations are highly sensitive and specific for known mutations, but interpretation of results is complex and generally requires posttest counseling.	
Treatment	Interventions in women who are *BRCA* mutation carriers include earlier, more frequent, or intensive cancer screening; risk-reducing medications (e.g., tamoxifen, raloxifene); and risk-reducing surgery (e.g., mastectomy, salpingo-oophorectomy).	
Balance of benefits and harms	In women whose family history is associated with an increased risk of potentially harmful *BRCA* mutations, the net benefit of genetic testing and early intervention is moderate.	In women whose family history is not associated with an increased risk of potentially harmful *BRCA* mutations, the net benefit of genetic testing and early intervention ranges from minimal to potentially harmful.
Other relevant USPSTF recommendations	The USPSTF has made recommendations on medications for the reduction of breast cancer risk and screening for ovarian cancer. These recommendations are available at http://www.uspreventiveservicestaskforce.org.	

NOTE: *For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, go to http://www.uspreventiveservicestaskforce.org/.*

USPSTF = U.S. Preventive Services Task Force.

for potentially harmful *BRCA* mutations are small to moderate.

USPSTF ASSESSMENT

For women whose family history is associated with an increased risk of potentially harmful mutations in the *BRCA1* or *BRCA2* gene, there is moderate certainty that the net benefit of testing for potentially harmful *BRCA* mutations and early intervention is moderate.

For women whose family history is not associated with an increased risk of potentially harmful mutations in the *BRCA1* or *BRCA2* gene, there is moderate certainty that the net benefit of testing for potentially harmful *BRCA* mutations and early intervention ranges from minimal to potentially harmful.

Clinical Considerations

PATIENT POPULATION

This recommendation applies to asymptomatic women who have not been diagnosed with *BRCA*-related cancer.

Women who have one or more family members with a known potentially harmful mutation in the *BRCA1* or *BRCA2* gene should be offered genetic counseling and testing.

The USPSTF recognizes the potential importance of further evaluating women who have a diagnosis of breast or ovarian cancer. Some women receive genetic testing as part of a cancer evaluation at the time of diagnosis of breast cancer. The USPSTF did not review the appropriate use of *BRCA* testing in the evaluation of women who are newly diagnosed with breast cancer. That assessment is part of disease management and is beyond the scope of this recommendation. Women who have been diagnosed with breast cancer in the past and who did not receive *BRCA* testing as part of their cancer care but have a family history of breast or ovarian cancer should be encouraged to discuss further evaluation with their clinician.

These recommendations do not apply to men, although male family members may be identified for testing during evaluation.

FAMILY HISTORY SCREENING AND RISK ASSESSMENT

Mutations in the *BRCA* genes cluster in families, exhibiting an autosomal dominant pattern of transmission in maternal or paternal lineage. During standard elicitation of family history information from patients, primary care clinicians should ask about specific types of cancer, primary cancer sites, which family members were affected, relatives with multiple types of primary cancer, and the age at diagnosis and sex of affected family members.

For women who have at least one family member with breast, ovarian, or other types of *BRCA*-related cancer, primary care clinicians may use one of several brief familial risk stratification tools to determine the need for in-depth genetic counseling.

Although several risk tools are available, the tools evaluated by the USPSTF include the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, and FHS-7; these tools may be viewed online at http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing).[10-19] The Referral Screening Tool (available at http://www.breastcancergenescreen.org) and FHS-7 are the simplest and quickest to administer. All of these tools seem to be clinically useful predictors of which women should be referred for genetic counseling because of increased risk of potentially harmful *BRCA* mutations (most sensitivity estimates were greater than 85%), although some models have been evaluated in only one study.[9,20] To determine which patients would benefit from *BRCA* risk assessment, primary care clinicians should not use general breast cancer risk assessment models (e.g., the National Cancer Institute Breast Cancer Risk Assessment Tool, which is based on the Gail model) because they are not designed to determine which women should receive genetic counseling or *BRCA* testing.

In general, these tools elicit information about factors that are associated with increased likelihood of *BRCA* mutations. Family history factors associated with increased likelihood of potentially harmful *BRCA* mutations include breast cancer diagnosis before 50 years of age, bilateral breast cancer, presence of breast and ovarian cancer, presence of breast cancer in one or more male family members, multiple cases of breast cancer in the family, one or more family members with two primary types of *BRCA*-related cancer, and Ashkenazi Jewish ethnicity. The USPSTF recognizes that each risk assessment tool has limitations, and found insufficient comparative evidence to recommend one tool over another. The USPSTF also found insufficient evidence to support a specific risk threshold for referral for testing.

GENETIC COUNSELING

Genetic counseling about *BRCA* mutation testing may be done by trained health professionals, including trained primary care clinicians. Several professional organizations describe the skills and training necessary to provide comprehensive genetic counseling. The process of genetic counseling includes detailed kindred analysis and risk assessment for potentially harmful *BRCA* mutations; education about the possible results of testing and their implications; identification of affected family members who may be preferred candidates for testing; outlining options for screening, risk-reducing medications, or surgery for eligible patients; and follow-up counseling for interpretation of test results.

BRCA MUTATION TESTING

Adequate evidence suggests that current genetic sequencing tests can accurately detect *BRCA* mutations. Testing for *BRCA* mutations should be done only when an individual has a personal or family history that suggests an inherited cancer susceptibility, when an individual has access to a health professional who is trained to provide genetic counseling and interpret test results, and when test results will aid in decision making. Initial testing of a family member who has breast or ovarian cancer is the preferred strategy in most cases, but it is reasonable to test if no affected relative is available. It is essential that before testing, the individual is fully informed about the implications of testing and has expressed a desire for it.

The type of mutation analysis required depends on family history. Individuals from families with known mutations or from ethnic groups in which certain mutations are more common (e.g., Ashkenazi Jewish women) can be tested for these specific mutations.

Individuals without linkages to families or groups with known mutations receive more comprehensive testing. In these cases, when possible, testing should begin with a relative who has breast or ovarian cancer to determine whether affected family members have a clinically significant mutation.

Tests for *BRCA* mutations are highly sensitive and specific for known mutations, but interpretation of results is complex and generally requires posttest counseling. Test results for genetic mutations are reported as positive (i.e., potentially harmful mutation detected), variants of uncertain clinical significance, uninformative-negative, or true-negative. Women who have relatives with known *BRCA* mutations can be reassured about their inherited risk of a potentially harmful mutation if the results are negative (i.e., a true negative). Some studies suggest increased breast cancer risk in some women with true-negative results.[21-24] However, a comprehensive meta-analysis conducted for the USPSTF that included these studies found that breast cancer risk is generally not increased in women with true-negative results.[9] An uninformative-negative result occurs when a woman's test does not detect a potentially harmful mutation but no relatives have been tested or no mutations have been detected in tested relatives. Available tests may not be able to identify mutations in these families. Risk of breast cancer is increased in women with uninformative-negative results.[9]

TIMING OF SCREENING

Consideration of screening for potentially harmful *BRCA* mutations should begin once women have reached the age of consent (18 years). Primary care clinicians should periodically assess all patients for changes in family history (e.g., comprehensive review at least every five to 10 years[25]).

INTERVENTIONS FOR WOMEN WHO ARE *BRCA* MUTATION CARRIERS

Interventions that may reduce risk of cancer or cancer-related death in women who are *BRCA* mutation carriers include earlier, more frequent, or intensive cancer screening; risk-reducing medications (e.g., tamoxifen or raloxifene); and risk-reducing surgery (e.g., mastectomy or salpingo-oophorectomy). However, the strength of evidence varies across the types of interventions.

Evidence is lacking on the effect of intensive screening for *BRCA*-related cancer on clinical outcomes in women who are *BRCA* mutation carriers. Medications, such as tamoxifen and raloxifene, have been shown to reduce the incidence of invasive breast cancer in high-risk women in the general population, but they have not been studied specifically in women who are *BRCA* mutation carriers.[9,20,26]

In high-risk women and those who are *BRCA* mutation carriers, cohort studies of risk-reducing surgery (mastectomy and salpingo-oophorectomy) showed substantially reduced risk of breast or ovarian cancer. Breast cancer risk was reduced by 85% to 100% with mastectomy[27-29] and by 37% to 100% with oophorectomy, and ovarian cancer risk was reduced by 69% to 100% with oophorectomy or salpingo-oophorectomy.[26] Salpingo-oophorectomy was also associated with a 55% relative reduction in all-cause mortality (as measured during the course of the study) in women with *BRCA1* or *BRCA2* mutations and without a history of breast cancer.[27]

OTHER APPROACHES TO PREVENTION

The USPSTF recommendations on medications for breast cancer risk reduction are available on the USPSTF website (http://www.uspreventiveservicestaskforce.org).

The USPSTF recommends against screening for ovarian cancer in women. This recommendation does not apply to women with known genetic mutations that increase their risk of ovarian cancer (e.g., *BRCA* mutations).

USEFUL RESOURCES

The National Cancer Institute Cancer Genetics Services Directory provides a list of professionals who offer services related to cancer genetics, including cancer risk assessment, genetic counseling, and genetic susceptibility testing (available at http://www.cancer.gov/cancertopics/genetics/directory).

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The "Other Considerations," "Discussion," "Update of Previous USPSTF Recommendation," and "Recommendations of Others" sections of this recommendation statement are available at http://www.uspreventiveservicestaskforce.org/Page/Topic/recommendation-summary/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing.

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