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%).3-8 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.3

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
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. 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. 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.

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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.8 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.8

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 23). 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 mastectomy27-29 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 USPSTF recommendations are independent of the U.S. government. They do not represent the views of the Agency for Healthcare Research and Quality, the U.S. Department of Health and Human Services, or the U.S. Public Health Service.

REFERENCES