Annals of Internal Medicine | Clinical Guideline

Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, MPH, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 2005 U.S. Preventive Services Task Force (USPSTF) recommendation on genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility.

Methods: The USPSTF reviewed the evidence on risk assessment, genetic counseling, and genetic testing for potentially harmful BRCA mutations in asymptomatic women with a family history of breast or ovarian cancer but no personal history of cancer or known potentially harmful BRCA mutations in their family. The USPSTF also reviewed interventions aimed at reducing the risk for BRCA-related cancer in women with potentially harmful BRCA mutations, including intensive cancer screening, medications, and risk-reducing surgery.

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

Recommendation: The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 of several screening tools designed to identify a family history that may be associated with an increased risk for 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 for potentially harmful mutations in the *BRCA1* or *BRCA2* genes. (D recommendation)

Ann Intern Med. www.annals.org

For author affiliation, see end of text.

* For a list of the members of the USPSTF, see the Appendix (available at www.annals.org).

This article was published online first at www.annals.org on 24 December 2013.

The U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

Summary of Recommendations and Evidence

The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 of several screening tools designed to identify a family history that may be associated with an increased risk for 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 for potentially harmful mutations in the *BRCA1* or *BRCA2* genes. (D recommendation)

See the Clinical Considerations section for additional information on screening tools.

See the **Figure** for a summary of the recommendation and suggestions for clinical practice.

See also:

Print

Related article 1

Summary for Patients 2

Web-Only

Supplement

Figure. **Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: clincal summary of U.S. Preventive Services Task Force recommendation.**

Annals of Internal Medicine

U.S. Preventive Services TASK FORCE
www.USPreventiveServicesTaskForce.org

RISK ASSESSMENT, GENETIC COUNSELING, AND GENETIC TESTING FOR BRCA-RELATED CANCER IN WOMEN CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Women who have not been diagnosed with BRCA-related cancer and who have no signs or symptoms of the disease	
Recommendation	Screen women whose family history may be associated with an increased risk for 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 for 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 age 50 years, bilateral breast cancer, family history of breast and ovarian cancer, presence of breast cancer in ≥1 male family member, multiple cases of breast cancer in the family, ≥1 family member with 2 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 for potentially harmful mutations, followed by genetic counseling by suitably trained health care providers 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 or raloxifene); and risk-reducing surgery (e.g., mastectomy or salpingo-oophorectomy).	
Balance of Benefits and Harms	In women whose family history is associated with an increased risk for 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 for potentially harmful BRCA mutations, the net benefit of genetic testing and early intervention ranges from small to moderate.
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 www.uspreventiveservicestaskforce.org.	

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

Appendix Table 1 describes the USPSTF grades, and **Appendix Table 2** describes the USPSTF classification of levels of certainty about net benefit (both tables are available at www.annals.org).

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 2.74% 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 for breast cancer increases to 45% to 65% by age 70 years if there are clinically significant mutations in either BRCA gene (3, 4). Mutations in the *BRCA1* gene increase ovarian cancer risk to 39% by age 70 years, and *BRCA2* mutations increase ovarian cancer risk to 10% to 17% by age 70 years (3, 4). In the general population, these mutations occur in an estimated 1 in 300 to 500 women (0.2% to 0.3%) (5–8). In a meta-analysis con-

ducted 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 for potentially harmful mutations, followed by genetic counseling from suitably trained health care providers 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 for potentially harmful mutations in the *BRCA1* or *BRCA2* genes, 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 for potentially harmful mutations in the *BRCA1* or *BRCA2* genes, 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 for potentially harmful mutations in the *BRCA1* or *BRCA2* genes, 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 for potentially harmful mutations in the *BRCA1* or *BRCA2* genes, 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 Under Consideration

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

Women who have 1 or more family members with a known potentially harmful mutation in the *BRCA1* or *BRCA2* genes 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 providers 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 1 family member with breast, ovarian, or other types of BRCA-related cancer, primary care providers may use 1 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 (**Table 1**), Manchester Scoring System (**Table 2**), Referral Screening Tool (**Table 3**), Pedigree Assessment Tool (**Table 4**), and FHS-7 (**Table 5**) (10–19). The Referral Screening Tool (available at 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 due to increased risk for potentially harmful BRCA mutations (most sensitivity estimates were >85%), although some models have been evaluated in only 1 study (9, 20). To determine which patients would benefit from BRCA risk assessment, primary care providers should not use general breast cancer risk assessment models (for example, 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 age 50 years, bilateral breast cancer, presence of breast and ovarian cancer, presence of breast cancer in 1 or more male family members, multiple cases of breast cancer in the family, 1 or more family mem-

Table 1. **Ontario Family History Assessment Tool***

Risk Factor	Points
Breast and ovarian cancer	
Mother	10
Sibling	7
Second-/third-degree relative	5
Breast cancer relative	
Parent	4
Sibling	3
Second-/third-degree relative	2
Male relative (add to above)	2
Breast cancer characteristics	
Onset at age 20–29 y	6
Onset at age 30–39 y	4
Onset at age 40–49 y	2
Premenopausal/perimenopausal	2
Bilateral/multifocal	3
Ovarian cancer relative	
Mother	7
Sibling	4
Second-/third-degree relative	3
Age at ovarian cancer onset	
<40 y	6
40–60 y	4
>60 y	2
Age at prostate cancer onset	
<50 y	1
Age at colon cancer onset	
<50 y	1
Family total	
Referral†	≥10

* From reference 19.
† Referral with a score of ≥10 corresponds to doubling of lifetime risk for breast cancer (22%).

bers with 2 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 providers. 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.

Table 2. **Manchester Scoring System***

Risk Factor	*BRCA1* Score	*BRCA2* Score
Age at onset of female breast cancer†		
<30 y	6	5
30–39 y	4	4
40–49 y	3	3
50–59 y	2	2
≥60 y	1	1
Age at onset of male breast cancer†		
<60 y	5‡	8§
≥60 y	5‡	5§
Age at onset of ovarian cancer†		
<60 y	8	5
≥60 y	5	5
Pancreatic cancer	0	1
Age at onset of prostate cancer†		
<60 y	0	2
≥60 y	0	1

* From reference 13. Developed so that a score of 10 in either column or a combined score of 15 for both columns would be equivalent to a 10% chance of identifying a *BRCA1* or *BRCA2* mutation.
† For relatives in direct lineage.
‡ If *BRCA2* tested.
§ If *BRCA1* tested.

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 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

Table 3. **Referral Screening Tool***

Risk Factor	Breast Cancer at Age ≤50 y	Ovarian Cancer at Any Age
Yourself		
Mother		
Sister		
Daughter		
Mother's side		
Grandmother		
Aunt		
Father's side		
Grandmother		
Aunt		
≥2 cases of breast cancer after age 50 y on the same side of the family		
Male breast cancer at any age in any relative		
Jewish ancestry		

* From reference 16. A patient completes the checklist if she has a family history of breast or ovarian cancer and receives a referral if she checks ≥2 items.

Table 4. **Pedigree Assessment Tool***

Risk Factor	Score†
Breast cancer at age ≥50 y	3
Breast cancer at age <50 y	4
Ovarian cancer at any age	5
Male breast cancer at any age	8
Ashkenazi Jewish heritage	4

* From reference 17. A score of ≥8 is the optimum referral threshold.
† For every family member with a breast or ovarian cancer diagnosis, including second- or third-degree relatives.

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 (for example, 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 (that is, 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 for a potentially harmful mutation if the results are negative (that is, 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 for breast cancer is increased in women with uninformative-negative results (9).

Table 5. **FHS-7***

Did any of your first-degree relatives have breast or ovarian cancer?
Did any of your relatives have bilateral breast cancer?
Did any man in your family have breast cancer?
Did any woman in your family have breast and ovarian cancer?
Did any woman in your family have breast cancer before age 50 y?
Do you have 2 or more relatives with breast and/or ovarian cancer?
Do you have 2 or more relatives with breast and/or bowel cancer?

* From reference 18. One positive response initiates referral.

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 providers should periodically assess all patients for changes in family history (for example, comprehensive review at least every 5 to 10 years [25]).

Interventions for Women Who Are BRCA Mutation Carriers

Interventions that may reduce risk for cancer or cancer-related death in women who are BRCA mutation carriers include earlier, more frequent, or intensive cancer screening; risk-reducing medications (for example, tamoxifen or raloxifene); and risk-reducing surgery (for example, 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 for 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 Web site (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 for ovarian cancer (for example, 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 sus-

ceptibility testing (available at www.cancer.gov/search/geneticsservices).

Other Considerations

Although some studies have reported that women prefer in-person genetic counseling, telephone- or computer-based counseling may be considered for women who would not otherwise have access to these services.

Research Needs and Gaps

Research on risk assessment and testing for BRCA mutations has focused on short-term outcomes for highly selected women in referral centers. Additional studies are needed, including comparative effectiveness trials of approaches to risk screening and strategies to improve access to genetic counseling and BRCA testing for high-risk individuals.

Another unresolved question is what specific training is needed (for persons other than trained genetic counselors) to provide genetic counseling. It would be helpful to understand which methods of delivery of genetic counseling are most effective, including those that can increase access to genetic counseling in rural or other settings. Trials comparing types of providers and protocols could address these questions.

What happens after patients are identified as high-risk in clinical settings is unknown. The consequences of genetic testing for individuals and their relatives require more study. Well-designed investigations using standardized measures and diverse study populations are needed.

An expanded database or registry of patients receiving genetic counseling for inherited breast and ovarian cancer susceptibility or who are tested for BRCA mutations would provide useful information about predictors of cancer and response to interventions. Additional data are needed from women of varying socioeconomic, racial, and ethnic groups.

For women who are mutation carriers, studies about the effectiveness of intensive cancer screening and risk-reducing medications and the effects of age at intervention on improving long-term outcomes are needed. This research would increase knowledge of the relative benefits and harms of interventions that are provided on the basis of genetic risk information.

Discussion

Burden of Disease

Breast cancer is the second most common cancer in women in the United States and is the second leading cause of cancer death (30, 31). In 2013, an estimated 232 340 women in the United States will be diagnosed with breast cancer and 39 620 women will die of the disease (32). According to lifetime risk estimates for the general population, 12.3% of women will develop breast cancer during their lives and 2.74% will die of it (2).

Ovarian cancer is the fifth leading cause of cancer death in women in the United States (31), accounting for an estimated 22 240 new cases and 14 030 deaths in 2013 (33). According to lifetime risk estimates for the general population, 1.4% of women will develop ovarian cancer during their lives and 1.0% will die of it (2).

Estimates of the prevalence of potentially harmful BRCA mutations vary by population. The estimated prevalence is 0.2% to 0.3% in the general population of women (5–8), 6.0% in women with cancer onset before age 40 years (8, 34, 35), and 2.1% in the general population of Ashkenazi Jewish women (36–39). In a meta-analysis of studies in which recruitment was based on family history of breast or ovarian cancer, *BRCA1* mutation prevalence was 13.6%, *BRCA2* mutation prevalence was 7.9%, and prevalence of either mutation was 19.8% (9).

Scope of Review

This recommendation applies to women who have no signs or symptoms of BRCA-related cancer. For its updated evidence review, the USPSTF considered risk assessment, genetic counseling, and genetic testing for potentially harmful *BRCA1* or *BRCA2* mutations in asymptomatic women with a family history of breast or ovarian cancer but no personal history of cancer or known potentially harmful BRCA mutations in their family. The USPSTF also reviewed interventions aimed at reducing the risk for BRCA-related cancer in women with potentially harmful BRCA mutations, including intensive cancer screening (for example, earlier and more frequent mammography or magnetic resonance imaging of the breast), medications (for example, tamoxifen or raloxifene), and risk-reducing surgery (for example, mastectomy or oophorectomy). Studies about patients with current or past breast or ovarian cancer were excluded unless they were designed to address screening issues in women without cancer (for example, retrospective or case–control studies).

Accuracy of Familial Risk Assessment

The USPSTF reviewed several tools that could be used in primary care settings to predict individual risk for breast cancer and potentially harmful BRCA mutations.

Tools specifically designed to determine risk for BRCA-related cancer are primarily intended for use by nongeneticist health care providers to guide referral to genetic counselors for more definitive evaluation. Models that have been validated in studies include the Ontario Family History Assessment Tool (**Table 1**), Manchester Scoring System (**Table 2**), Referral Screening Tool (**Table 3**), Pedigree Assessment Tool (**Table 4**), and FHS-7 (**Table 5**) (10–19). In general, these tools elicit information about factors associated with increased likelihood of BRCA mutations. They are clinically useful predictors of which women should be referred for genetic counseling because of increased risk for potentially harmful BRCA mutations (most sensitivity estimates were >85%), although some models have been evaluated in only 1 study (9, 20). The

USPSTF recognizes that each risk assessment tool has limitations and found insufficient evidence to recommend one tool over another.

Accuracy of BRCA Mutation Testing

The type of mutation analysis done depends on family history. Individuals from families with known mutations or from ethnic groups with common mutations (for example, Ashkenazi Jewish women) can be tested specifically for these mutations. The sensitivity and specificity of analysis techniques are measured by individual clinical laboratories and are not publicly available. Individuals without linkages to families or groups with known mutations receive more comprehensive testing. In these cases, guidelines recommend initial testing of a relative with known breast or ovarian cancer, when possible, to check for the presence of clinically significant mutations.

Effectiveness of BRCA Mutation Testing and Early Detection and Treatment

To understand the potential benefits and harms of genetic counseling, the USPSTF reviewed 18 studies (40–57) published since its previous review. Studies generally reported positive (or no negative) psychological effects, increased accuracy of risk perception, or decreased intention to have genetic testing.

Genetic counseling significantly decreased breast cancer worry in 8 studies (44–46, 48, 50, 53–55). Three studies (41, 44, 49) reported decreased or no changes in general anxiety and depression after genetic counseling, whereas other studies found no significant differences in anxiety scores (48, 50). However, 1 of these studies noted an increase in state anxiety scores after genetic counseling (44). Eight studies published since 2004 reported improved accuracy of risk perception after genetic counseling (41, 42, 44–47, 49, 50, 52). Two studies reported decreased intention to have genetic testing after genetic counseling (45, 46).

Interventions that may reduce risk for cancer in women who are BRCA mutation carriers include: earlier, more frequent, or intensive cancer screening; use of selective estrogen receptor modulators as risk-reducing medications (for example, tamoxifen or raloxifene); and risk-reducing surgery (for example, mastectomy or salpingo-oophorectomy).

Evidence is lacking on the effect of intensive screening for BRCA-related cancer on clinical outcomes in women who are BRCA mutation carriers.

Selective estrogen receptor modulators reduced the incidence of invasive breast cancer in several randomized, controlled trials (58–64), although clinical trials of tamoxifen and raloxifene have not been conducted specifically in women who are BRCA mutation carriers. In a meta-analysis of trials published to date (26, 65), tamoxifen and raloxifene reduced the incidence of estrogen receptor–positive invasive breast cancer, with 7 fewer events per 1000 women for tamoxifen (4 trials) and 9 fewer events per 1000 women for raloxifene (2 trials), assuming 5 years of treatment. Selective estrogen receptor modulators do not reduce risk for estrogen receptor–negative breast cancer, which includes 69% of breast cancer cases associated with *BRCA1* mutations and 16% associated with *BRCA2* mutations (66).

In cohort studies of high-risk women and those who are BRCA mutation carriers, risk-reducing surgery (for example, mastectomy or salpingo-oophorectomy) substantially reduced risk for breast or ovarian cancer. Mastectomy reduced breast cancer risk by 85% to 100%, and oophorectomy or salpingo-oophorectomy reduced ovarian cancer risk by 69% to 100% and breast cancer risk by 37% to 100% (9). In 1 fair-quality prospective cohort study (27), 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* and *BRCA2* mutations without a history of breast cancer. Breast cancer risk reduction associated with oophorectomy was more pronounced in women who were premenopausal at the time of surgery (27, 67).

Potential Harms of Cancer Screening and Treatment

Intensive screening for breast and ovarian cancer is associated with false-positive results, unnecessary imaging, and unneeded surgery. In 2 studies comparing mammography with magnetic resonance imaging for breast cancer screening in which 18% to 100% of study participants were BRCA mutation carriers, mammography was associated with higher false-positive rates (14% vs. 5.5% in the first round of screening; $P < 0.001$ [68]; 15% vs. 11% in another study [69]) and more false-negative results (12 vs. 1 case in the first round of screening; 12 vs. 4 cases in subsequent rounds [68]). In a retrospective analysis of a cohort of women with potentially harmful BRCA mutations or first-degree relatives with BRCA mutations, those who were screened with mammography were more likely to have unneeded imaging than those who were screened with magnetic resonance imaging; however, rates of unneeded biopsy were similar (69).

Risk-reducing medications (for example, tamoxifen or raloxifene) can increase risk for thromboembolic events (4 to 7 events per 1000 women over 5 years). Tamoxifen increased the risk for endometrial cancer (4 to 5 cases per 1000 women) compared with placebo or raloxifene, and it also increased risk for cataracts (15 per 1000 women) compared with raloxifene (26, 63).

Data on the long-term physical harms of risk-reducing mastectomy are limited. In high-risk women having risk-reducing mastectomy with immediate reconstruction, 21% in 1 series had complications (for example, hematoma, contracture, or implant rupture) (70). In another series, 64% reported postsurgical symptoms (for example, numbness, pain, tingling, infection, swelling, breast hardness, bleeding, organizing hematoma, failed reconstruction, breathing problems, thrombosis, and pulmonary embo-

lism) (71). After risk-reducing oophorectomy, 5% of women in 1 study had postsurgical complications (for example, wound infection, bladder or uterine perforation, or small-bowel obstruction) (72).

Seven observational studies provided data on psychological distress due to risk-reducing mastectomy (71, 73–76) or oophorectomy (25, 77). In 1 study of 90 women who had risk-reducing bilateral mastectomy (73, 74), there were significant reductions in scores for anxiety and sexual pleasure and no significant differences in depression scores, body image concerns, or other measures. In another study (75), there were no significant differences in psychological measures between women who had risk-reducing mastectomy and a reference sample that did not have the procedure. Ten years after risk-reducing mastectomy, most women in another study reported that their family lives were unchanged, but 39% reported negative effects on spousal relationships because of decreased sensation and changed body appearance (76). After risk-reducing salpingo-oophorectomy, premenopausal women reported significant worsening of vasomotor symptoms and decreased sexual function (77).

Estimate of Magnitude of Net Benefit

For women whose family history is associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes, the USPSTF found adequate evidence that the benefits of testing, detection, and early intervention are moderate. For women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes, the USPSTF found adequate evidence that the benefits of testing, detection, and early intervention are few to none. The USPSTF found adequate evidence that the overall harms of testing, detection, and early intervention are small to moderate.

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

How Does Evidence Fit With Biological Understanding?

The *BRCA1* and *BRCA2* genes are tumor suppressor genes. Mutations of these genes have been linked to hereditary breast and ovarian cancer. Risks for breast, ovarian, and other types of BRCA-related cancer are greatly increased in patients who have inherited potentially harmful *BRCA1* or *BRCA2* mutations. Genetic testing may identify such mutations. Several options are available to manage cancer risk in patients who are found to be mutation carriers.

Response to Public Comments

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from 2 April through 29 April 2013. In response to comments, the USPSTF clarified that this recommendation statement applies to women. It also expanded the recommendation to include women who have family members with tubal or peritoneal (in addition to breast or ovarian) cancer. The USPSTF clarified that it recognizes the potential importance of further evaluating women who have a diagnosis of breast or ovarian cancer; however, that assessment is part of disease management and is beyond the scope of this recommendation.

The USPSTF added that it found insufficient evidence to recommend one risk assessment tool over another or to support a specific risk threshold for referral for genetic counseling and BRCA testing. It also added a compilation of risk assessment tools (**Tables 1 to 5**). Although the preferred BRCA testing strategy is initial testing of a family member with breast or ovarian cancer, the USPSTF clarified that it is reasonable to start testing in an unaffected individual if no affected relative is available. Because of the complexity of BRCA test results, the USPSTF also suggests posttest counseling. It also clarified and updated information on BRCA testing, other resources, and recommendations of other groups.

Update of Previous USPSTF Recommendation

In 2005, the USPSTF recommended that women whose family history is associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes be referred for genetic counseling and evaluation for BRCA testing. It also recommended against routine referral for genetic counseling or routine BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes (78).

This recommendation statement reaffirms the USPSTF's previous recommendation. Since 2005, family history risk stratification tools have been developed and validated for use in primary care practice to guide referral for BRCA genetic counseling (**Tables 1 to 5**). In addition, the potential benefits and harms of medications for breast cancer risk reduction have been studied for longer follow-up periods, and more information is available about the potential psychological effects of genetic counseling and risk-reducing surgery.

Recommendations of Other Groups

The National Comprehensive Cancer Network provides specific criteria for genetic counseling and testing (1). The American Congress of Obstetricians and Gynecologists recommends genetic risk assessment for women who have more than a 20% to 25% risk for an inherited predisposition to breast and ovarian cancer and states that it

may be helpful for patients with more than a 5% to 10% risk (79). The American Society of Clinical Oncology recommends genetic testing when there is personal or family history suggestive of genetic cancer susceptibility, the test can be adequately interpreted, and the results will aid in diagnosis or medical management of the patient or family member who has hereditary risk for cancer. It also recommends genetic testing only when pretest and posttest counseling are included (80). The National Society of Genetic Counselors has issued practice guidelines for risk assessment and genetic counseling for hereditary breast and ovarian cancer. It recommends that genetic testing should be offered to individuals with a personal or family history suggestive of an inherited cancer syndrome, when the test can be adequately interpreted, if testing will influence medical management of the patient or relative, when potential benefits outweigh potential risks, if testing is voluntary, and when the individual seeking testing or a legal proxy can provide informed consent (81). The European Society for Medical Oncology recommends that all patients who may be referred for BRCA testing should first complete informed consent and genetic counseling and patients who are mutation carriers should be encouraged to advise close family members to obtain genetic counseling (82). The Society of Gynecologic Oncologists recommends genetic risk assessment for individuals with a personal risk of more than approximately 20% to 25% for an inherited predisposition to cancer and states that it may be helpful for patients with more than approximately 5% to 10% risk. Genetic testing for cancer predisposition requires informed consent that should encompass pretest education and counseling about the risks, benefits, and limitations of testing, including the implications of both positive and negative genetic test results (83).

From the U.S. Preventive Services Task Force, Rockville, Maryland.

Financial Support: The USPSTF is an independent, voluntary body. The U.S. Congress mandates that the Agency for Healthcare Research and Quality support the operations of the USPSTF.

Potential Conflicts of Interest: Disclosure forms from USPSTF members can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M13-2747.

Requests for Single Reprints: Reprints are available from the USPSTF Web site (www.uspreventiveservicestaskforce.org).

References

1. **Lindor NM, McMaster ML, Lindor CJ, Greene MH; National Cancer Institute, Division of Cancer Prevention, Community Oncology and Prevention Trials Research Group.** Concise handbook of familial cancer susceptibility syndromes - second edition. J Natl Cancer Inst Monogr. 2008:1-93. [PMID: 18559331]

2. **Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, et al, eds.** SEER Cancer Statistics Review, 1975–2010. Bethesda, MD: National Cancer Institute; 2013. Accessed at http://seer.cancer.gov/csr/1975_2010 on 14 November 2013.

3. **Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al.** Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003;72:1117-30. [PMID: 12677558]

4. **Chen S, Parmigiani G.** Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007;25:1329-33. [PMID: 17416853]

5. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. Br J Cancer. 2000;83:1301-8. [PMID: 11044354]

6. **Antoniou AC, Gayther SA, Stratton JF, Ponder BA, Easton DF.** Risk models for familial ovarian and breast cancer. Genet Epidemiol. 2000;18:173-90. [PMID: 10642429]

7. **Antoniou AC, Pharoah PD, McMullan G, Day NE, Stratton MR, Peto J, et al.** A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. Br J Cancer. 2002;86:76-83. [PMID: 11857015]

8. **Peto J, Collins N, Barfoot R, Seal S, Warren W, Rahman N, et al.** Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. J Natl Cancer Inst. 1999;91:943-9. [PMID: 10359546]

9. **Nelson HD, Fu R, Goddard K, Priest Mitchell J, Okinaka-Hu L, Pappas M, et al.** Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation. Evidence synthesis no. 101. AHRQ publication no. 12-05164-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2013.

10. **Panchal SM, Ennis M, Canon S, Bordeleau LJ.** Selecting a BRCA risk assessment model for use in a familial cancer clinic. BMC Med Genet. 2008;9:116. [PMID: 19102775]

11. **Parmigiani G, Chen S, Iversen ES Jr, Friebel TM, Finkelstein DM, Anton-Culver H, et al.** Validity of models for predicting BRCA1 and BRCA2 mutations. Ann Intern Med. 2007;147:441-50. [PMID: 17909205]

12. **Oros KK, Ghadirian P, Maugard CM, Perret C, Paredes Y, Mes-Masson AM, et al.** Application of BRCA1 and BRCA2 mutation carrier prediction models in breast and/or ovarian cancer families of French Canadian descent. Clin Genet. 2006;70:320-9. [PMID: 16965326]

13. **Evans DG, Eccles DM, Rahman N, Young K, Bulman M, Amir E, et al.** A new scoring system for the chances of identifying a BRCA1/2 mutation outperforms existing models including BRCAPRO. J Med Genet. 2004;41:474-80. [PMID: 15173236]

14. **Barcenas CH, Hosain GM, Arun B, Zong J, Zhou X, Chen J, et al.** Assessing BRCA carrier probabilities in extended families. J Clin Oncol. 2006;24:354-60. [PMID: 16421416]

15. **Antoniou AC, Hardy R, Walker L, Evans DG, Shenton A, Eeles R, et al.** Predicting the likelihood of carrying a BRCA1 or BRCA2 mutation: validation of BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester scoring system using data from UK genetics clinics. J Med Genet. 2008;45:425-31. [PMID: 18413374]

16. **Bellcross CA, Lemke AA, Pape LS, Tess AL, Meisner LT.** Evaluation of a breast/ovarian cancer genetics referral screening tool in a mammography population. Genet Med. 2009;11:783-9. [PMID: 19752737]

17. **Hoskins KF, Zwaagstra A, Ranz M.** Validation of a tool for identifying women at high risk for hereditary breast cancer in population-based screening. Cancer. 2006;107:1769-76. [PMID: 16967460]

18. **Ashton-Prolla P, Giacomazzi J, Schmidt AV, Roth FL, Palmero EI, Kalakun L, et al.** Development and validation of a simple questionnaire for the identification of hereditary breast cancer in primary care. BMC Cancer. 2009;9:283. [PMID: 19682358]

19. **Gilpin CA, Carson N, Hunter AG.** A preliminary validation of a family history assessment form to select women at risk for breast or ovarian cancer for referral to a genetics center. Clin Genet. 2000;58:299-308. [PMID: 11076055]

20. **Nelson H, Pappas M, Zakher B, Mitchell J, Okinaka-Hu L, Fu R.** Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: a systematic review to update the U.S. Preventive Services Task Force recommendation. Ann Intern Med. 2013.

21. **Gronwald J, Cybulski C, Lubinski J, Narod SA.** Phenocopies in breast cancer 1 (BRCA1) families: implications for genetic counselling [Letter]. J Med Genet. 2007;44:e76. [PMID: 17400795]
22. **Rowan E, Poll A, Narod SA.** A prospective study of breast cancer risk in relatives of BRCA1/BRCA2 mutation carriers. J Med Genet. 2007;44:e89. [PMID: 17673443]
23. **Smith A, Moran A, Boyd MC, Bulman M, Shenton A, Smith L, et al.** Phenocopies in BRCA1 and BRCA2 families: evidence for modifier genes and implications for screening. J Med Genet. 2007;44:10-15. [PMID: 17079251]
24. **Vos JR, de Bock GH, Teixeira N, van der Kolk DM, Jansen L, Mourits MJ, et al.** Proven non-carriers in BRCA families have an earlier age of onset of breast cancer. Eur J Cancer. 2013. [PMID: 23490645]
25. **Finch A, Metcalfe KA, Chiang J, Elit L, McLaughlin J, Springate C, et al.** The impact of prophylactic salpingo-oophorectomy on quality of life and psychological distress in women with a BRCA mutation. Psychooncology. 2013;22: 212-9. [PMID: 21913283]
26. **Nelson HD, Smith ME, Griffin JC, Fu R.** Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013;158:604-14. [PMID: 23588749]
27. **Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al.** Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010;304:967-75. [PMID: 20810374]
28. **Skytte AB, Crüger D, Gerster M, Laenkholm AV, Lang C, Brøndum-Nielsen K, et al.** Breast cancer after bilateral risk-reducing mastectomy. Clin Genet. 2011;79:431-7. [PMID: 21199491]
29. **Evans DG, Gaarenstroom KN, Stirling D, Shenton A, Maehle L, Dørum A, et al.** Screening for familial ovarian cancer: poor survival of BRCA1/2 related cancers. J Med Genet. 2009;46:593-7. [PMID: 18413372]
30. **Centers for Disease Control and Prevention.** Breast Cancer Statistics. Atlanta, GA: Centers for Disease Control and Prevention; 2013. Accessed at www.cdc.gov/cancer/breast/statistics on 14 November 2013.
31. **Centers for Disease Control and Prevention, National Cancer Institute, North American Association of Central Cancer Registries.** United States Cancer Statistics: 1999–2010 Cancer Incidence and Mortality Data. Atlanta, GA: Centers for Disease Control and Prevention; 2013. Accessed at http://apps.nccd.cdc.gov/uscs on 9 December 2013.
32. **National Cancer Institute.** Breast Cancer. Bethesda, MD: National Cancer Institute; 2013. Accessed at www.cancer.gov/cancertopics/types/breast on 14 November 2013.
33. **National Cancer Institute.** Ovarian Cancer. Bethesda, MD: National Cancer Institute; 2013. Accessed at www.cancer.gov/cancertopics/types/ovarian on 14 November 2013.
34. **FitzGerald MG, MacDonald DJ, Krainer M, Hoover I, O'Neil E, Unsal H, et al.** Germ-line BRCA1 mutations in Jewish and non-Jewish women with early-onset breast cancer. N Engl J Med. 1996;334:143-9. [PMID: 8531968]
35. **Malone KE, Daling JR, Neal C, Suter NM, O'Brien C, Cushing-Haugen K, et al.** Frequency of BRCA1/BRCA2 mutations in a population-based sample of young breast carcinoma cases. Cancer. 2000;88:1393-402. [PMID: 10717622]
36. **Fodor FH, Weston A, Bleiweiss IJ, McCurdy LD, Walsh MM, Tartter PI, et al.** Frequency and carrier risk associated with common BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer patients. Am J Hum Genet. 1998; 63:45-51. [PMID: 9634504]
37. **Hartge P, Struewing JP, Wacholder S, Brody LC, Tucker MA.** The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews. Am J Hum Genet. 1999;64:963-70. [PMID: 10090881]
38. **Metcalfe KA, Poll A, Royer R, Llacuachaqui M, Tulman A, Sun P, et al.** Screening for founder mutations in BRCA1 and BRCA2 in unselected Jewish women. J Clin Oncol. 2010;28:387-91. [PMID: 20008623]
39. **Roa BB, Boyd AA, Volcik K, Richards CS.** Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. Nat Genet. 1996; 14:185-7. [PMID: 8841191]
40. **Armstrong K, Micco E, Carney A, Stopfer J, Putt M.** Racial differences in the use of BRCA1/2 testing among women with a family history of breast or ovarian cancer. JAMA. 2005;293:1729-36. [PMID: 15827311]
41. **Roshanai AH, Rosenquist R, Lampic C, Nordin K.** Does enhanced information at cancer genetic counseling improve counselees' knowledge, risk perception, satisfaction and negotiation of information to at-risk relatives?—a randomized study. Acta Oncol. 2009;48:999-1009. [PMID: 19636983]
42. **Matloff ET, Moyer A, Shannon KM, Niendorf KB, Col NF.** Healthy women with a family history of breast cancer: impact of a tailored genetic counseling intervention on risk perception, knowledge, and menopausal therapy decision making. J Womens Health (Larchmt). 2006;15:843-56. [PMID: 16999640]
43. **Bloom JR, Stewart SL, Chang S, You M.** Effects of a telephone counseling intervention on sisters of young women with breast cancer. Prev Med. 2006;43: 379-84. [PMID: 16916540]
44. **Braithwaite D, Sutton S, Mackay J, Stein J, Emery J.** Development of a risk assessment tool for women with a family history of breast cancer. Cancer Detect Prev. 2005;29:433-9. [PMID: 16055276]
45. **Helmes AW, Culver JO, Bowen DJ.** Results of a randomized study of telephone versus in-person breast cancer risk counseling. Patient Educ Couns. 2006;64:96-103. [PMID: 16427245]
46. **Bowen DJ, Burke W, Culver JO, Press N, Crystal S.** Effects of counseling Ashkenazi Jewish women about breast cancer risk. Cultur Divers Ethnic Minor Psychol. 2006;12:45-56. [PMID: 16594854]
47. **Mikkelsen EM, Sunde L, Johansen C, Johnsen SP.** Risk perception among women receiving genetic counseling: a population-based follow-up study. Cancer Detect Prev. 2007;31:457-64. [PMID: 18061369]
48. **Mikkelsen EM, Sunde L, Johansen C, Johnsen SP.** Psychosocial consequences of genetic counseling: a population-based follow-up study. Breast J. 2009;15:61-8. [PMID: 19120380]
49. **Pieterse AH, Ausems MG, Spreeuwenberg P, van Dulmen S.** Longer-term influence of breast cancer genetic counseling on cognitions and distress: smaller benefits for affected versus unaffected women. Patient Educ Couns. 2011;85: 425-31. [PMID: 21316181]
50. **Hopwood P, Wonderling D, Watson M, Cull A, Douglas F, Cole T, et al.** A randomised comparison of UK genetic risk counselling services for familial cancer: psychosocial outcomes. Br J Cancer. 2004;91:884-92. [PMID: 15305197]
51. **Kelly KM, Senter L, Leventhal H, Ozakinci G, Porter K.** Subjective and objective risk of ovarian cancer in Ashkenazi Jewish women testing for BRCA1/2 mutations. Patient Educ Couns. 2008;70:135-42. [PMID: 17988821]
52. **Gurmankin AD, Domchek S, Stopfer J, Fels C, Armstrong K.** Patients' resistance to risk information in genetic counseling for BRCA1/2. Arch Intern Med. 2005;165:523-9. [PMID: 15767527]
53. **Bennett P, Wilkinson C, Turner J, Brain K, Edwards RT, Griffith G, et al.** Psychological factors associated with emotional responses to receiving genetic risk information. J Genet Couns. 2008;17:234-41. [PMID: 18259848]
54. **Brain K, Parsons E, Bennett P, Cannings-John R, Hood K.** The evolution of worry after breast cancer risk assessment: 6-year follow-up of the TRACE study cohort. Psychooncology. 2011;20:984-91. [PMID: 20677331]
55. **Fry A, Cull A, Appleton S, Rush R, Holloway S, Gorman D, et al.** A randomised controlled trial of breast cancer genetics services in South East Scotland: psychological impact. Br J Cancer. 2003;89:653-9. [PMID: 12915873]
56. **Smerecnik CM, Mesters I, Verweij E, de Vries NK, de Vries H.** A systematic review of the impact of genetic counseling on risk perception accuracy. J Genet Couns. 2009;18:217-28. [PMID: 19291376]
57. **Bennett P, Wilkinson C, Turner J, Edwards RT, France B, Griffith G, et al.** Factors associated with intrusive cancer-related worries in women undergoing cancer genetic risk assessment. Fam Cancer. 2009;8:159-65. [PMID: 19011994]
58. **Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, et al.** Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 2005;97:1652-62. [PMID: 16288118]
59. **Powles TJ, Ashley S, Tidy A, Smith IE, Dowsett M.** Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst. 2007;99:283-90. [PMID: 17312305]
60. **Veronesi U, Maisonneuve P, Rotmensz N, Bonanni B, Boyle P, Viale G, et al; Italian Tamoxifen Study Group.** Tamoxifen for the prevention of breast cancer: late results of the Italian Randomized Tamoxifen Prevention Trial among women with hysterectomy. J Natl Cancer Inst. 2007;99:727-37. [PMID: 17470740]
61. **Cuzick J, Forbes JF, Sestak I, Cawthorn S, Hamed H, Holli K, et al; International Breast Cancer Intervention Study I Investigators.** Long-term results of tamoxifen prophylaxis for breast cancer—96-month follow-up of the randomized IBIS-I trial. J Natl Cancer Inst. 2007;99:272-82. [PMID: 17312304]

62. **Grady D, Cauley JA, Geiger MJ, Kornitzer M, Mosca L, Collins P, et al; Raloxifene Use for The Heart Trial Investigators.** Reduced incidence of invasive breast cancer with raloxifene among women at increased coronary risk. J Natl Cancer Inst. 2008;100:854-61. [PMID: 18544744]

63. **Lippman ME, Cummings SR, Disch DP, Mershon JL, Dowsett SA, Cauley JA, et al.** Effect of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis categorized by breast cancer risk. Clin Cancer Res. 2006;12:5242-7. [PMID: 16951244]

64. **Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al; National Surgical Adjuvant Breast and Bowel Project.** Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. Cancer Prev Res (Phila). 2010;3:696-706. [PMID: 20404000]

65. **Nelson HD, Fu R, Humphrey L, Smith M, Griffin JC, Nygren P.** Comparative Effectiveness of Medications to Reduce Risk of Primary Breast Cancer in Women. Comparative effectiveness review no. 17. Rockville, MD: Agency for Healthcare Research and Quality; 2009.

66. **Kurian AW, Gong GD, John EM, Johnston DA, Felberg A, West DW, et al.** Breast cancer risk for noncarriers of family-specific BRCA1 and BRCA2 mutations: findings from the Breast Cancer Family Registry. J Clin Oncol. 2011; 29:4505-9. [PMID: 22042950]

67. **Eisen A, Lubinski J, Klijn J, Moller P, Lynch HT, Offit K, et al.** Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. J Clin Oncol. 2005;23:7491-6. [PMID: 16234515]

68. **Kriege M, Brekelmans CT, Boetes C, Muller SH, Zonderland HM, Obdeijn IM, et al; Dutch MRI Screening (MRISC) Study Group.** Differences between first and subsequent rounds of the MRISC breast cancer screening program for women with a familial or genetic predisposition. Cancer. 2006;106: 2318-26. [PMID: 16615112]

69. **Le-Petross HT, Whitman GJ, Atchley DP, Yuan Y, Gutierrez-Barrera A, Hortobagyi GN, et al.** Effectiveness of alternating mammography and magnetic resonance imaging for screening women with deleterious BRCA mutations at high risk of breast cancer. Cancer. 2011;117:3900-7. [PMID: 21365619]

70. **Contant CM, Menke-Pluijmers MB, Seynaeve C, Meijers-Heijboer EJ, Klijn JG, Verhoog LC, et al.** Clinical experience of prophylactic mastectomy followed by immediate breast reconstruction in women at hereditary risk of breast cancer (HB(O)C) or a proven BRCA1 and BRCA2 germ-line mutation. Eur J Surg Oncol. 2002;28:627-32. [PMID: 12359199]

71. **Metcalfe KA, Esplen MJ, Goel V, Narod SA.** Psychosocial functioning in women who have undergone bilateral prophylactic mastectomy. Psychooncology. 2004;13:14-25. [PMID: 14745742]

72. **Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, et al.** Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2002;346:1609-15. [PMID: 12023992]

73. **Brandberg Y, Arver B, Johansson H, Wickman M, Sandelin K, Liljegren A.** Less correspondence between expectations before and cosmetic results after risk-reducing mastectomy in women who are mutation carriers: a prospective study. Eur J Surg Oncol. 2012;38:38-43. [PMID: 22032910]

74. **Brandberg Y, Sandelin K, Erikson S, Jurell G, Liljegren A, Lindblom A, et al.** Psychological reactions, quality of life, and body image after bilateral prophylactic mastectomy in women at high risk for breast cancer: a prospective 1-year follow-up study. J Clin Oncol. 2008;26:3943-9. [PMID: 18711183]

75. **Gahm J, Wickman M, Brandberg Y.** Bilateral prophylactic mastectomy in women with inherited risk of breast cancer—prevalence of pain and discomfort, impact on sexuality, quality of life and feelings of regret two years after surgery. Breast. 2010;19:462-9. [PMID: 20605453]

76. **Wasteson E, Sandelin K, Brandberg Y, Wickman M, Arver B.** High satisfaction rate ten years after bilateral prophylactic mastectomy - a longitudinal study. Eur J Cancer Care (Engl). 2011;20:508-13. [PMID: 20597955]

77. **Finch A, Metcalfe KA, Chiang JK, Elit L, McLaughlin J, Springate C, et al.** The impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual function in women who carry a BRCA mutation. Gynecol Oncol. 2011;121:163-8. [PMID: 21216453]

78. **Nelson HD, Huffman LH, Fu R, Harris EL; U.S. Preventive Services Task Force.** Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med. 2005;143:362-79. [PMID: 16144895]

79. **American College of Obstetricians and Gynecologists.** ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. Obstet Gynecol. 2009;113:957-66. [PMID: 19305347]

80. **Robson ME, Storm CD, Weitzel J, Wollins DS, Offit K; American Society of Clinical Oncology.** American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. J Clin Oncol. 2010; 28:893-901. [PMID: 20065170]

81. **Berliner JL, Fay AM, Cummings SA, Burnett B, Tillmanns T.** NSGC practice guideline: risk assessment and genetic counseling for hereditary breast and ovarian cancer. J Genet Couns. 2013;22:155-63. [PMID: 23188549]

82. **Balmaña J, Díez O, Rubio IT, Cardoso F; ESMO Guidelines Working Group.** BRCA in breast cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2011;22 Suppl 6:vi31-4. [PMID: 21908500]

83. **Lancaster JM, Powell CB, Kauff ND, Cass I, Chen LM, Lu KH, et al; Society of Gynecologic Oncologists Education Committee.** Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol. 2007;107:159-62. [PMID: 17950381]

Appendix: U.S. Preventive Services Task Force

Members of the U.S. Preventive Services Task Force at the time this recommendation was finalized† are Virginia A. Moyer, MD, MPH, *Chair* (American Board of Pediatrics, Chapel Hill, North Carolina); Michael L. LeFevre, MD, MSPH, *Co-Vice Chair* (University of Missouri School of Medicine, Columbia, Missouri); Albert L. Siu, MD, MSPH, *Co-Vice Chair* (Mount Sinai School of Medicine, New York, and James J. Peters Veterans Affairs Medical Center, Bronx, New York); Linda Ciofu Baumann, PhD, RN (University of Wisconsin, Madison, Wisconsin); Kirsten Bibbins-Domingo, PhD, MD (University of California, San Francisco, San Francisco, California); Susan J. Curry, PhD (University of Iowa College of Public Health, Iowa City, Iowa); Mark Ebell, MD, MS (University of Georgia, Athens, Georgia); Glenn Flores, MD (University of Texas Southwestern, Dallas, Texas); Francisco A.R. García, MD, MPH (Pima County Department of Health, Tucson, Arizona); Adelita Gonzales Cantu, RN, PhD (University of Texas Health Science Center, San Antonio, Texas); David C. Grossman, MD, MPH (Group Health Cooperative, Seattle, Washington); Jessica Herzstein, MD, MPH (Air Products, Allentown, Pennsylvania); Wanda K. Nicholson, MD, MPH, MBA (University of North Carolina School of Medicine, Chapel Hill, North Carolina); Douglas K. Owens, MD, MS (Veterans Affairs Palo Alto Health Care System, Palo Alto, and Stanford University, Stanford, California); William R. Phillips, MD, MPH (University of Washington, Seattle, Washington); and Michael P. Pignone, MD, MPH (University of North Carolina, Chapel Hill, North Carolina).

† For a list of current Task Force members, go to www.uspreventiveservicestaskforce.org/members.htm.

Appendix Table 1. **What the USPSTF Grades Mean and Suggestions for Practice**

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer/provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer/provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Appendix Table 2. **USPSTF Levels of Certainty Regarding Net Benefit**

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; and lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: the limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings that are not generalizable to routine primary care practice; and a lack of information on important health outcomes. More information may allow an estimation of effects on health outcomes.

* The USPSTF defines *certainty* as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general primary care population. The USPSTF assigns a certainty level on the basis of the nature of the overall evidence available to assess the net benefit of a preventive service.