Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility: Recommendation Statement: United States Preventive Services Task Force

United States Preventive Services Task Force

Citation

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Abstract

Figure 3

Agency for Healthcare Research and Quality

Figure 2

US Department of Health and Human Services

SUMMARY OF RECOMMENDATIONS

The U.S. Preventive Services Task Force (USPSTF) recommends against routine referral for genetic counseling or routine breast cancer susceptibility gene (BRCA) testing for women whose family history is not associated with an increased risk for deleterious mutations in breast cancer susceptibility gene 1 (BRCA1) or breast cancer susceptibility gene 2 (BRCA2) . D recommendation.

The USPSTF found fair evidence that women without certain specific family history patterns, termed here “increased risk family history” (see Clinical Considerations for a definition) have a low risk for developing breast or ovarian cancer associated with BRCA1 or BRCA2 mutations. Thus, any benefit to routine screening of these women for BRCA1 or BRCA2 mutations, or routine referral for genetic counseling, would be small or zero.

The USPSTF found fair evidence regarding important adverse ethical, legal, and social consequences that could result from routine referral and testing of these women. Interventions such as prophylactic surgery, chemoprevention, or intensive screening have known harms. The USPSTF estimated that the magnitude of these potential harms is small or greater.

The USPSTF concluded that the potential harms of routine referral for genetic counseling or BRCA testing in these women outweigh the benefits.

The USPSTF recommends that women whose family history is associated with an increased risk for deleterious mutations

in BRCA1 or BRCA2 genes be referred for genetic counseling and evaluation for BRCA testing. B recommendation.

The USPSTF found fair evidence that women with certain specific family history patterns ("increased risk family history") have an increased risk for developing breast or ovarian cancer associated with BRCA1 or BRCA2 mutations. The USPSTF determined that these women would benefit from genetic counseling that allows informed decision-making about testing and further prophylactic treatment. This counseling should be done by suitably trained health care providers. There is insufficient evidence to determine the benefits of chemoprevention or intensive screening in improving health outcomes in these women if they test positive for deleterious BRCA1 or BRCA2 mutations. However, there is fair evidence that prophylactic surgery for these women significantly decreases breast and ovarian cancer incidence. Thus, the potential benefits of referral and discussion of testing and prophylactic treatment for these women may be substantial.

The USPSTF also found insufficient evidence regarding important adverse ethical, legal, and social consequences that could result from referral and testing of high risk women. Prophylactic surgery is associated with known harms. The USPSTF estimated that the magnitude of these potential harms is small.

The USPSTF concluded that the benefits of referring women with an increased-risk family history to suitably trained healthcare providers outweigh the harms.

CLINICAL CONSIDERATIONS

These recommendations apply to women who have not received a diagnosis of breast or ovarian cancer. They do not apply to women with a family history of breast or ovarian cancer that includes a relative with a known deleterious mutation in BRCA1 or BRCA2 genes; these women should be referred for genetic counseling. These recommendations do not apply to men.

Although there currently are no standardized referral criteria, women with an increased- risk family history should be considered for genetic counseling to further evaluate their potential risks.

Certain specific family history patterns are associated with an increased risk for deleterious mutations in the BRCA1 or BRCA2 gene. Both maternal and paternal family histories are important. For non-Ashkenazi Jewish women, these patterns include 2 first-degree relatives with breast cancer, one of whom was diagnosed at age 50 or younger; a combination of 3 or more first- or second-degree relatives with breast cancer, regardless of age of diagnosis; a combination of both breast and ovarian cancer among first- and second- degree relatives; a first-degree relative with bilateral breast cancer; a combination of 2 or more first- or second-degree relatives with ovarian cancer, regardless of age of diagnosis; a first- or second-degree relative with both breast and ovarian cancer, at any age; a history of breast cancer in a male relative.

For women of Ashkenazi Jewish heritage, an increased risk family history includes any first-degree relative (or 2 second-degree relatives on the same side of the family) with breast or ovarian cancer.

About 2% of adult women in the general population have an increased-risk family history as defined here. Women without one of these family history patterns have a low probability of having a deleterious mutation in BRCA1 or BRCA2 genes.

Computational tools are available to predict the risk for clinically important BRCA mutations (ie, BRCA mutations associated with the presence of breast cancer, ovarian cancer, or both), but these tools have not been verified in the general population. There is no empirical evidence concerning what level of risk for a BRCA mutation merits referral for genetic counseling.

Not all women with a potentially deleterious BRCA mutation will develop breast or ovarian cancer. In a woman who has a clinically important BRCA mutation, the probability of developing breast or ovarian cancer by the age of 70 is estimated to be 35% to 84% for breast cancer and 10% to 50% for ovarian cancer.

Appropriate genetic counseling helps women make informed decisions, can improve their knowledge and perception of absolute risk for breast and ovarian cancer, and can often reduce anxiety. Genetic counseling includes elements of counseling; risk assessment; pedigree analysis; and, in some cases, recommendations for testing for BRCA mutations in affected family members, the presenting patient, or both. It is best delivered by a suitably trained healthcare provider.

A BRCA test typically is ordered by a physician. When done in concert with genetic counseling, the test assures the

linkage of testing with appropriate management decisions. Genetic testing may lead to potential adverse ethical, legal, and social consequences, such as insurance and employment discrimination; these issues should be discussed in the context of genetic counseling and evaluation for testing.

Among women with BRCA1 or BRCA2 mutations, prophylactic mastectomy or oophorectomy decreases the incidence of breast and ovarian cancer; there is inadequate evidence for mortality benefits. Chemoprevention with selective estrogen receptor modulators may decrease incidence of estrogen receptor-positive cancers; however, it is also associated with adverse effects, such as pulmonary embolism, deep vein thrombosis, and endometrial cancer. Most breast cancer associated with BRCA1 mutations is estrogen-receptor negative and thus is not prevented by tamoxifen. Intensive screening with mammography has poor sensitivity, and there is no evidence of benefit of intensive screening for women with BRCA1 or BRCA2 gene mutations. Magnetic resonance imaging (MRI) may detect more cases of cancer, but the effect on mortality is not clear.

Women with an increased risk family history are at risk not only for deleterious BRCA1 or BRCA2 mutations, but potentially for other unknown mutations as well. Women with an increased-risk family history who have negative test results for BRCA1 and BRCA2 mutations may also benefit from surgical prophylaxis.

The USPSTF has made recommendations on mammography screening for breast cancer, screening for ovarian cancer, and chemoprevention of breast cancer, which can be accessed at: http://www.preventiveservices.ahrq.gov.

DISCUSSION

Breast and ovarian cancer are associated with a family history of these conditions. Approximately 5% to 10% of women with breast cancer have a mother or sister with breast cancer, and up to 20% have a first-degree or a second-degree relative with breast cancer.[1,2,3,4,5,6] Germline mutations in two genes, BRCA1 and BRCA2, have been associated with an increased risk for breast cancer and ovarian cancer.[7, 8] Specific BRCA mutations (founder mutations) are clustered among certain ethnic groups, such as Ashkenazi Jews, and among families in the Netherlands, Iceland, and Sweden. [1]

Several characteristics are associated with an increased likelihood of BRCA mutations.[1, 9,10,11,12] These include breast cancer diagnosed at an early age, bilateral breast cancer, history of both breast and ovarian cancer, presence of breast cancer in 1 or more male family members, multiple cases of breast cancer in the family, both breast and ovarian cancer in the family, 1 or more family members with 2 primary cancers, and Ashkenazi Jewish background. No direct measures of the prevalence of clinically important BRCA1 or BRCA2 mutations in the general, non-Jewish U.S. population have been published; however, models have estimated it to be about 1 in 300 to 500.[13,14,15,16] Prevalence estimates in a large study of individuals from referral populations with various levels of family history range from 3.9% (no breast cancer diagnosed in relatives younger than age 50 and no ovarian cancer) to 16.4% (breast cancer diagnosed in a relative younger than age 50 and ovarian cancer diagnosed at any age).[17]

Penetrance is the probability of developing breast or ovarian cancer among women who have a BRCA1 or BRCA2 mutation. Published reports of penetrance describe estimates of BRCA1 and BRCA2 mutations ranging from 35% to 84% for breast cancer and 10% to 50% for ovarian cancer, calculated to age 70 years, for non-Ashkenazi Jewish women or those unselected for ethnicity .[1, 13, 14, 18,19,20,21,22] Among Ashkenazi Jewish women, penetrance estimates range from 26% to 81% for breast cancer and 10% to 46% for ovarian cancer.[1, 23,24,25,26,27,28,29] Estimates are higher for relatives of women with cancer diagnosed at younger ages, for women from families with greater numbers of affected relatives (when based on data from families selected for breast and ovarian cancer), and when certain methods of analysis are used.

A systematic review of the evidence found no population-based randomized controlled trials of risk assessment and BRCA mutation testing using the outcomes of incidence of breast and ovarian cancer or cause-specific mortality.[1] The USPSTF therefore examined the chain of evidence for accuracy of risk assessment tools, efficacy of preventive interventions, and the harms of screening and interventions.

Although several tools to predict risk for deleterious BRCA mutations have been developed from data on previously tested women, no studies of their effectiveness in a screening population in a primary care setting are available.[30] These risk tools include Myriad Genetic Laboratories model, the Couch model, BRCAPRO and the Tyrer model.[1] Much of the data used to develop the models are from women with existing cancer, and their applicability to asymptomatic, cancer-free women in the general population is unknown.

Three tools have been developed to guide primary care clinicians in assessing risk and guiding referral: the Family History Risk Assessment Tool (FHAT), the Manchester scoring system, and the Risk Assessment in Genetics (RAGs) tool.[31] The sensitivity and specificity of FHAT for a clinically important BRCA1 or BRCA2 mutation were 94% and 51%, respectively. The Manchester scoring system was developed in the United Kingdom to predict deleterious BRCA1 or BRCA2 mutations at the 10% likelihood level and had an 87% sensitivity and a 66% specificity.[32] The RAGs tool, a computer program designed to support assessment and management of family breast and ovarian cancer in primary care settings,[33] is used to assign patients to low risk (<10%), moderate risk (10%-25%), or high risk (>25%) categories. Primary care clinicians can then manage recommendations of reassurance, referral to a breast clinic, or referral to a geneticist on the basis of the patient's respective risk categories. [34]

The interventions that can be offered to a woman with a deleterious BRCA1 or BRCA2 mutation or other increased risk for hereditary breast cancer include intensive screening, chemoprevention, prophylactic mastectomy or oophorectomy, or a combination. Overall, evidence on the efficacy of intensive surveillance of BRCA1 and BRCA2 carriers to reduce morbidity or mortality is insufficient. Recent descriptive studies report increased risk for interval cancer (cancer occurring between mammograms) in BRCA-positive patients with and without previous cancer who are receiving annual mammographic screening. This indicates that annual mammography may miss aggressive cancer in carriers of the BRCA mutation.[1]

Good evidence shows that MRI has higher sensitivity for detecting breast cancer among women with a BRCA1 or BRCA2 mutation than does mammography, clinical breast examination, or ultrasound. One study compared these screening methods in 236 Canadian women 25 to 65 years of age who had BRCA1 or BRCA2 mutations.[35] The women underwent 1 to 3 annual screening examinations including MRI, mammography, and ultrasonography, and received clinical breast examinations provided every 6 months. The researchers found that MRI was more sensitive for detecting breast cancers (sensitivity 77%; specificity 95.4%) than mammography (sensitivity 36%, specificity 99.8%), ultrasonography (sensitivity 33%, specificity 96%), or clinical breast examination alone (sensitivity 9%, specificity 99.3%). However, use of MRI, ultrasonography, and mammography in combination had the highest sensitivity, 95%. The effect of this increased detection on morbidity and mortality remains unclear. Expert groups recommend intensive screening for breast cancer in patients with BRCA mutation.[36]

The evidence is also insufficient to determine the morbidity and mortality effects of intensive screening for ovarian cancer among women with BRCA1 or BRCA2 mutations. One study in which 1,610 women with a family history of ovarian cancer were screened with transvaginal ultrasonography showed a high rate of false-positive results (only 3 of 61 women with abnormal scans had ovarian cancer).[37]

Good quality evidence from 4 randomized controlled trials shows that prophylactic tamoxifen reduces the risk for estrogen receptor-positive breast cancer in women without previous breast cancer.[38, 39] A meta-analysis of these trials showed a relative risk for total breast cancer of 0.62 (95% CI, .46 to .83).[1] Further analysis of the largest of these trials showed a possible reduction in breast cancer incidence for women with BRCA2 mutations but not those with BRCA1 mutations, possibly because women with BRCA1 mutations had predominantly estrogen receptor-negative tumors. Conclusions are difficult to draw because of the small number of breast cancers in this analysis.[40]

Fair quality evidence is available on the effectiveness of prophylactic surgery to prevent breast and ovarian cancer. Cohort studies of prophylactic surgery have several methodologic limitations that should be considered when interpreting and generalizing their results, such as selection bias, retrospective study design, lack of a control group for estimation of benefit-attributable outcome in the untreated group, and inability to define risk reduction attributable to mastectomy in patients electing both mastectomy and oophorectomy.[41] Four published studies (2 of fair quality, 2 that did not meet USPSTF quality criteria) of prophylactic bilateral mastectomy in high-risk women show a consistent 85% to 100% reduction in risk for breast cancer despite differences in study designs and comparison groups (for example, sisters[42], matched controls[43], a surveillance group[44], and penetrance models[45]. Four studies of prophylactic oophorectomy reported reduced risks for ovarian and breast cancer[46,47,48,49], although the number of cases was small and the confidence intervals for the only prospective study crossed 1.0 for both outcomes.[50] Overall, oophorectomy reduced ovarian cancer risk by 85% to 100%, and reduced

breast cancer risk by 53% to 68%.

No studies have described cancer incidence or mortality outcomes associated with genetic counseling, although 10 fair- to good-quality randomized controlled trials reported psychological and behavioral outcomes.[1] These studies examined the impact of genetic counseling on worrying about breast cancer, anxiety, depression, perception of cancer risk, and intention to participate in genetic testing. Studies were conducted in highly selected samples of women and results may not be generalizable to a screening population. Five of 7 trials showed that breast cancer worry decreased after genetic counseling and 2 studies showed no significant effect.[1] Three studies reported decreased anxiety after genetic counseling and 3 reported no significant effect. One study reported decreased depression after genetic counseling and 4 found no significant effect.[1]Results of a meta-analysis show that genetic counseling significantly decreased generalized anxiety, although the reduction in psychological distress was not significant.[43] There is poor evidence (conflicting studies) regarding whether genetic counseling increases or decreases the accuracy of patients' risk perception.

The USPSTF examined the available evidence on harms of screening and intervention. Approximately 12% of high risk families without a BRCA1 or BRCA2 coding-region mutation may have other clinically important genomic rearrangements.[44] Approximately 13% of tests report mutations of unknown significance; however, the harms associated with such test results are not known.[45] Routine referral for genetic counseling and consideration of BRCA1 and BRCA2 testing clearly has important psychological, ethical, legal, and social implications, although they are not well quantified in the literature. Among these are the potential for burdening patients with the knowledge of mutations of unknown importance and the potential for affecting family members other than the individual patient. The potential harms of intensive screening include overdiagnosis and overtreatment. There is good quality evidence on the harms of prophylactic tamoxifen, [1] including thromboembolic events, endometrial cancer, and hot flashes. Fair quality evidence shows that prophylactic mastectomy can cause hematoma, infection, contracture, or implant rupture (with reconstruction); and that prophylactic oophorectomy can cause infection, bleeding, urinary tract or bowel injury, and premature menopause. Overall, the USPSTF estimates that the magnitude of these potential harms is at least small.

RESEARCH GAPS

Population studies are needed to determine the prevalence and penetrance of various mutations in the BRCA gene and the factors that influence penetrance for women with these mutations. Research has focused on highly selected women in referral centers and has generally reported short-term outcomes. Issues requiring additional study include the effectiveness of risk stratification and genetic counseling when delivered in different settings and by different types of providers, appropriate training for counselors, use of system supports, and patient acceptance of educational strategies. The impact of BRCA testing on ethical, legal, and social issues needs to be better clarified. We also need to understand the effect of genetic counseling on the emotions and behavior of the patient and her first-degree female relatives.

Enhanced screening with such methods as MRI needs to be better studied in high risk women. Future studies should examine the impact of intensive MRI screening on breast cancer mortality and on possible overtreatment. Studies specifically designed to examine the potential benefit of chemoprophylaxis in women with known deleterious BRCA mutations are essential to establish whether there are any effective alternatives to prophylactic surgery. There is a paucity of data on BRCA-associated ovarian cancer; further research in screening and management of women at high risk for ovarian cancer is needed. It would be helpful to develop and validate tools feasible for use in primary care practice that would help clinicians make appropriate referrals for genetic counseling.

RECOMMENDATIONS OF OTHER GROUPS

A few organizations have made recommendations on genetic susceptibility testing. Specific criteria for consideration of genetic evaluation, counseling, and mutation testing can be found in the references, below. The American College of Medical Genetics (ACMG) recommends risk assessment and genetic counseling prior to testing for BRCA1/BRCA2 mutations in individuals at increased risk, based on a personal or family history of breast and/or ovarian cancer.[54] In a previous guideline published in 1996, the ACMG recommended testing for BRCA1 mutations in high risk families and population screening of Ashkenazi Jewish individuals after discussion of test limitations and appropriate informed consent.[55] The National

Comprehensive Cancer Network recommends offering genetic susceptibility testing (after risk assessment and counseling) to individuals who meet the criteria for hereditary breast or ovarian cancer or both.[56] The American Society of Clinical Oncology recommends that genetic testing be offered when 1) an individual has a personal or family history that suggests a genetic cancer susceptibility and 2) the test can be adequately interpreted and its results will influence diagnosis or management of the patient or family members at risk for hereditary cancer.[57] The American College of Obstetricians and Gynecologists Committee Opinion on breast and ovarian cancer screening, written in 2000, recommends offering BRCA mutation testing to families in which multiple family members have had breast or ovarian cancer or in which a BRCA mutation has been found.[58]

MEMBERS OF THE USPSTF

Corresponding Author: Ned Calonge, MD, MPH, Chair, U.S. Preventive Services Task Force, c/o Program Director, USPSTF, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, e-mail: uspstf@ahrq.gov.

Members of the U.S. Preventive Services Task Force* are Alfred O. Berg, MD, MPH, Chair, USPSTF (Professor and Chair, Department of Family Medicine, University of Washington, Seattle, WA); Janet D. Allan, PhD, RN, CS, Vice-chair, USPSTF (Dean, School of Nursing, University of Maryland, Baltimore, Baltimore, MD); Ned Calonge, MD, MPH (Chief Medical Officer and State Epidemiologist, Colorado Department of Public Health and Environment, Denver, CO); Paul S. Frame, MD (Family Physician, Tri-County Family Medicine, Cohocton, NY, and Clinical Professor of Family Medicine, University of Rochester, Rochester, NY); Leon Gordis, MD, MPH, DrPH (Professor, Epidemiology Department, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD); Kimberly D. Gregory, MD, MPH, (Director, Women's Health Service Research and Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, CA); Russell Harris, MD, MPH (Professor of Medicine, Sheps Center for Health Services Research, University of North Carolina School of Medicine, Chapel Hill, NC); Mark S. Johnson, MD, MPH (Professor and Chair, Department of Family Medicine, University of Medicine and Dentistry of New Jersey-New Jersey Medical School, Newark, NJ); Jonathan D. Klein, MD, MPH (Associate Professor, Department of Pediatrics, University of Rochester School of Medicine, Rochester, NY); Carol Loveland-Cherry, PhD, RN (Executive Associate Dean, Office of Academic Affairs, University of Michigan School of Nursing, Ann Arbor, MI); Virginia A. Moyer, MD, MPH (Professor, Department of Pediatrics, University of Texas Health Science Center, Houston, TX); Judith K. Ockene, PhD (Professor of Medicine and Chief of Division of Preventive and Behavioral Medicine, University of Massachusetts Medical School, Worcester, MA); Diana B. Petitti, MD, MPH (Senior Scientific Advisor for Health Policy and Medicine, Kaiser Permanente Southern California, Pasadena, CA); Albert L. Siu, MD, MSPH (Professor and Chairman, Brookdale Department of Geriatrics and Adult Development, Mount Sinai Medical Center, New York, NY); Steven M. Teutsch, MD, MPH (Executive Director, Outcomes Research and Management, Merck & Company, Inc., West Point, PA); and Barbara P. Yawn, MD, MSc (Director of Research, Olmstead Research Center, Rochester, MN).

*Members of the Task Force at the time this recommendation was finalized. For a list of current Task Force members, go to http://www.ahrq.gov/clinic/uspstfab.htm.

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APPENDIX A

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS AND RATINGS

The Task Force grades its recommendations according to one of 5 classifications (A, B, C, D, I) reflecting the strength

of evidence and magnitude of net benefit (benefits minus harms):

A. The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.

B. The USPSTF recommends that clinicians provide [the service] to eligible patients. The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.

C. The USPSTF makes no recommendation for or against routine provision of [the service]. The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.

D. The USPSTF recommends against routinely providing [the service] to asymptomatic patients. The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.

I. The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. Evidence that [the service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

APPENDIX B

U.S. PREVENTIVE SERVICES TASK FORCE STRENGTH OF OVERALL EVIDENCE

The USPSTF grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor):

Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

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Author Information

United States Preventive Services Task Force
Agency for Healthcare Research and Quality , US Department of Health and Human Services