Genetic Risk Assessment and *BRCA* Mutation Testing for Breast and Ovarian Cancer Susceptibility: Recommendation Statement

U.S. Preventive Services Task Force*

This statement summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations on genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility, along with the supporting scientific evidence. The complete information on which this statement is based, including evidence tables and references, is included in the evidence synthesis available through the USPSTF Web site (www.preventiveservices.ahrq.gov). The recommendation is also posted on the Web site of the National Guideline Clearinghouse (www.guideline.gov).

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*For a list of the members of the U.S. Preventive Services Task Force, see the Appendix.

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).*

This is a **grade D recommendation**. (See **Appendix Table 1** for a description of the USPSTF classification of recommendations.)

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.* (See **Appendix Table 2** for a description of the USPSTF classification of levels of evidence.)

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.

This is a **grade 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.

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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 health care 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, 1 of whom received the diagnosis at age 50 years or younger; a combination of 3 or more first- or second-degree relatives with breast cancer regardless of age at 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 at diagnosis; a first- or second-degree relative with both breast and ovarian cancer at any age; and 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 with none 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 (that is, *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 the level of risk for a *BRCA* mutation that 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 age 70 years 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 health care provider.

A *BRCA* test is typically 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 breast cancer; however, it is also associated with adverse effects, such as pulmonary embolism, deep venous 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 results on tests 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 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 (1–6). Germline mutations in 2 genes, *BRCA1* and *BRCA2*, have been associated with an increased risk for breast cancer and ovarian cancer (7, 8). Specific *BRCA* mutations (founder mu-

tations) 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, 9–12). 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 cases of cancer, 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 (13–16). Prevalence estimates in a large study of individuals from referral populations with various levels of family history ranged from 3.9% (no breast cancer diagnosed in relatives <50 years of age and no ovarian cancer) to 16.4% (breast cancer diagnosed in a relative <50 years of age and ovarian cancer diagnosed at any age) (17).

Penetrance is the probability of developing breast or ovarian cancer in 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, 18–22). Among Ashkenazi Jewish women, penetrance estimates range from 26% to 81% for breast cancer and 10% to 46% for ovarian cancer (1, 23–29). 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 primary care screening population are available (30). These risk tools include the 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 categories of low risk (<10%), moderate risk (10% to 25%), and high risk (>25%). 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 were 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 ultrasonography. One study compared these screening methods in 236 Canadian women 25 to 65 years of age who had *BRCA1* or *BRCA*2 mutations (35). The women underwent 1 to 3 annual screening examinations, including MRI, mammography, and ultrasonography, and received clinical breast examinations every 6 months. The researchers found that MRI was more sensitive for detecting breast cancer (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 the *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 1610 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, 0.46 to 0.83) (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 cancer cases 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 to have both mastectomy and oophorectomy (41). Four published studies (2 of fair quality and 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 (46–49), 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 showed that genetic counseling significantly decreased generalized anxiety, although the reduction in psychological distress was not significant (51). 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 (52). Approximately 13% of tests report mutations of unknown significance; however, the harms associated with such test results are not known (53). 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. The American College of Medical Genetics (ACMG) recommends risk assessment and genetic counseling before testing for *BRCA1*/*BRCA2* mutations in individuals at increased risk, based on a personal or family history of breast cancer, ovarian cancer, or both (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).

APPENDIX

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This list includes members of the Task Force at the time these recommendations were finalized. For a list of current Task Force members, go to www.ahrq.gov/clinic/uspstfab.htm.

Appendix Table 1. **U.S. Preventive Services Task Force Recommendations and Ratings***

Grade	Recommendation
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.*

* The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

Appendix Table 2. **U.S. Preventive Services Task Force Grades for Strength of Overall Evidence***

Grade	Definition
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

* The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence for a service on a three-point scale (good, fair, poor).

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Requests for Single Reprints: Reprints are available from the USPSTF Web site (www.preventiveservices.ahrq.gov) and in print through the Agency for Healthcare Research and Quality Publications Clearinghouse (800-358-9295).

References

1. **Nelson HD, Huffman LH, Fu R, Harris EL, Walker M, Bougatsos C.** Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility. Systematic Evidence Synthesis No. 37 (Prepared by the Oregon Evidence-based Practice Center under contract no. 290-02-0024). 2005. Available at www.ahrq.gov/clinic/uspstfix.htm.

2. **Yang Q, Khoury MJ, Rodriguez C, Calle EE, Tatham LM, Flanders WD.** Family history score as a predictor of breast cancer mortality: prospective data from the Cancer Prevention Study II, United States, 1982-1991. Am J Epidemiol. 1998;147:652-9. [PMID: 9554604]

3. **Colditz GA, Willett WC, Hunter DJ, Stampfer MJ, Manson JE, Hennekens CH, et al.** Family history, age, and risk of breast cancer. Prospective data from the Nurses' Health Study. JAMA. 1993;270:338-43. [PMID: 8123079]

4. **Slattery ML, Kerber RA.** A comprehensive evaluation of family history and breast cancer risk. The Utah Population Database. JAMA. 1993;270:1563-8. [PMID: 8371466]

5. **Johnson N, Lancaster T, Fuller A, Hodgson SV.** The prevalence of a family history of cancer in general practice. Fam Pract. 1995;12:287-9. [PMID: 8536831]

6. **Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA.** Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer. 1997;71:800-9. [PMID: 9180149]

7. **Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, et al.** A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science. 1994;266:66-71. [PMID: 7545954]

8. **Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, et al.** Identification of the breast cancer susceptibility gene BRCA2. Nature. 1995;378:789-92. [PMID: 8524414]

9. **Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, et al.** Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10, 000 individuals. J Clin Oncol. 2002;20:1480-90. [PMID: 11896095]

10. **Srivastava A, McKinnon W, Wood ME.** Risk of breast and ovarian cancer in women with strong family histories. Oncology (Williston Park). 2001;15:889-902; discussion 902, 905-7, 911-13. [PMID: 11499690]

11. **Shattuck-Eidens D, Oliphant A, McClure M, McBride C, Gupte J, Rubano T, et al.** BRCA1 sequence analysis in women at high risk for susceptibility mutations. Risk factor analysis and implications for genetic testing. JAMA. 1997; 278:1242-50. [PMID: 9333265]

12. **Couch FJ, DeShano ML, Blackwood MA, Calzone K, Stopfer J, Campeau L, et al.** BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. N Engl J Med. 1997;336:1409-15. [PMID: 9145677]

13. 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]

14. **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]

15. **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]

16. **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]

17. Myriad Genetic Laboratories, Inc. Accessed at www.myriadtests.com/home.htm on 30 April 2004.

18. **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]

19. **Brose MS, Rebbeck TR, Calzone KA, Stopfer JE, Nathanson KL, Weber BL.** Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Natl Cancer Inst. 2002;94:1365-72. [PMID: 12237282]

20. **Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, et al.** Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet. 1998;62:676-89. [PMID: 9497246]

21. **Hopper JL, Southey MC, Dite GS, Jolley DJ, Giles GG, McCredie MR, et al.** Population-based estimate of the average age-specific cumulative risk of breast cancer for a defined set of protein-truncating mutations in BRCA1 and BRCA2. Australian Breast Cancer Family Study. Cancer Epidemiol Biomarkers Prev. 1999;8:741-7. [PMID: 10498392]

22. **Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Kwan E, et al.** Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet. 2001;68: 700-10. [PMID: 11179017]

23. **King MC, Marks JH, Mandell JB.** Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003;302:643-6. [PMID: 14576434]

24. **Moslehi R, Chu W, Karlan B, Fishman D, Risch H, Fields A, et al.** BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. Am J Hum Genet. 2000;66:1259-72. [PMID: 10739756]

25. **Satagopan JM, Boyd J, Kauff ND, Robson M, Scheuer L, Narod S, et al.** Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Clin Cancer Res. 2002;8:3776-81. [PMID: 12473589]

26. **Satagopan JM, Offit K, Foulkes W, Robson ME, Wacholder S, Eng CM, et al.** The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev. 2001;10:467-73. [PMID: 11352856]

27. **Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, et al.** The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med. 1997;336:1401-8. [PMID: 9145676]

28. **Warner E, Foulkes W, Goodwin P, Meschino W, Blondal J, Paterson C, et al.** Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. J Natl Cancer Inst. 1999; 91:1241-7. [PMID: 10413426]

29. **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]

30. **Domchek SM, Eisen A, Calzone K, Stopfer J, Blackwood A, Weber BL.** Application of breast cancer risk prediction models in clinical practice. J Clin Oncol. 2003;21:593-601. [PMID: 12586794]

31. **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]

32. **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]

33. **Emery J, Walton R, Coulson A, Glasspool D, Ziebland S, Fox J.** Computer support for recording and interpreting family histories of breast and ovarian cancer in primary care (RAGs): qualitative evaluation with simulated patients. BMJ. 1999;319:32-6. [PMID: 10390458]

34. **Emery J, Walton R, Murphy M, Austoker J, Yudkin P, Chapman C, et al.** Computer support for interpreting family histories of breast and ovarian cancer in primary care: comparative study with simulated cases. BMJ. 2000;321:28-32. [PMID: 10875832]

35. **Warner E, Plewes DB, Hill KA, Causer PA, Zubovits JT, Jong RA, et al.** Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA. 2004;292:1317-25. [PMID: 15367553]

36. **Burke W, Petersen G, Lynch P, Botkin J, Daly M, Garber J, et al.** Recommendations for follow-up care of individuals with an inherited predisposition to cancer. I. Hereditary nonpolyposis colon cancer. Cancer Genetics Studies Consortium. JAMA. 1997;277:915-9. [PMID: 9062331]

37. **Bourne TH, Campbell S, Reynolds KM, Whitehead MI, Hampson J, Royston P, et al.** Screening for early familial ovarian cancer with transvaginal ultrasonography and colour blood flow imaging. BMJ. 1993;306:1025-9. [PMID: 8490496]

38. **Cuzick J, Forbes J, Edwards R, Baum M, Cawthorn S, Coates A, et al.** First results from the International Breast Cancer Intervention Study (IBIS-I): a ran-

domised prevention trial. Lancet. 2002;360:817-24. [PMID: 12243915]
39. **Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al.** Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90:1371-88. [PMID: 9747868]
40. **King MC, Wieand S, Hale K, Lee M, Walsh T, Owens K, et al.** Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA. 2001;286:2251-6. [PMID: 11710890]
41. **Klaren HM, van't Veer LJ, van Leeuwen FE, Rookus MA.** Potential for bias in studies on efficacy of prophylactic surgery for BRCA1 and BRCA2 mutation. J Natl Cancer Inst. 2003;95:941-7. [PMID: 12837830]
42. **Hartmann LC, Schaid DJ, Woods JE, Crotty TP, Myers JL, Arnold PG, et al.** Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med. 1999;340:77-84. [PMID: 9887158]
43. **Rebbeck TR, Friebel T, Lynch HT, Neuhausen SL, van 't Veer L, Garber JE, et al.** Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol. 2004; 22:1055-62. [PMID: 14981104]
44. **Meijers-Heijboer H, van Geel B, van Putten WL, Henzen-Logmans SC, Seynaeve C, Menke-Pluymers MB, et al.** Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2001;345:159-64. [PMID: 11463009]
45. **Hartmann LC, Sellers TA, Schaid DJ, Frank TS, Soderberg CL, Sitta DL, et al.** Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst. 2001;93:1633-7. [PMID: 11698567]
46. **Struewing JP, Watson P, Easton DF, Ponder BA, Lynch HT, Tucker MA.** Prophylactic oophorectomy in inherited breast/ovarian cancer families. J Natl Cancer Inst Monogr. 1995:33-5. [PMID: 8573450]
47. **Rebbeck TR, Levin AM, Eisen A, Snyder C, Watson P, Cannon-Albright L, et al.** Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. J Natl Cancer Inst. 1999;91:1475-9. [PMID: 10469748]
48. **Rebbeck TR.** Prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers. Eur J Cancer. 2002;38 Suppl 6:S15-7. [PMID: 12409058]
49. **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]
50. **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]
51. **Meiser B, Halliday JL.** What is the impact of genetic counselling in women at increased risk of developing hereditary breast cancer? A meta-analytic review. Soc Sci Med. 2002;54:1463-70. [PMID: 12061481]
52. **Unger MA, Nathanson KL, Calzone K, Antin-Ozerkis D, Shih HA, Martin AM, et al.** Screening for genomic rearrangements in families with breast and ovarian cancer identifies BRCA1 mutations previously missed by conformation-sensitive gel electrophoresis or sequencing. Am J Hum Genet. 2000;67:841-50. [PMID: 10978226]
53. **Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, et al.** Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10, 000 individuals. J Clin Oncol. 2002;20:1480-90. [PMID: 11896095]
54. **American College of Medical Genetics Foundation.** Genetic Susceptibility to Breast and Ovarian Cancer: Assessment, Counseling and Testing Guidelines. June 1998. Accessed at www.health.state.ny.us/nysdoh/cancer/obcancer/contents.htm on 4 March 2005.
55. **American College of Medical Genetics.** Statement on Population Screening for BRCA-1 Mutation in Ashkenazi Jewish Women. 1996. Accessed at www.acmg.net/resources/policies/pol-002.asp on 25 March 2005.
56. **National Comprehensive Cancer Network.** Clinical Practice Guidelines in Oncology. Genetic/Familial High Risk Assessment: Breast and Ovarian Cancer. 2005. Accessed at www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf on 4 March 2005.
57. American Society of Clinical Oncology Policy Statement Update: Genetic Testing for Cancer Susceptibility. 11 April 2003. J Clin Oncol. Accessed at www.asco.org/asco/downloads/GeneticTesting.pdf on 4 March 2005.
58. ACOG committee opinion. Breast-ovarian cancer screening. Number 239, August 2000. American College of Obstetricians and Gynecologists. Committee on genetics. Int J Gynaecol Obstet. 2001;75:339-40. [PMID: 11794298]