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Genetic Risk Assessment and *BRCA* Mutation Testing for Breast and Ovarian Cancer Susceptibility: Evidence Synthesis

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Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) and Evidence Syntheses through its Evidence-based Practice Program. With guidance from the U.S. Preventive Services Task Force* (USPSTF) and input from Federal partners and primary care specialty societies, the Oregon Evidence-based Practice Center systematically reviews the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, and chemoprevention, in the primary care setting. The SERs and Evidence Syntheses—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services—serve as the foundation for the recommendations of the USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the "Methods" section of each SER and Evidence Synthesis.

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We welcome written comments on this Evidence Synthesis. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 540 Gaither Road, Suite 3000, Rockville, MD 20850, or e-mail uspstf@ahrq.gov.

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*The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services--including screening, counseling, and chemoprevention--in the primary care setting. AHRQ convened the current USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.

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Structured Abstract

Context: Breast cancer is the second most common cancer in women in the U.S. and is the second leading cause of cancer death. Although less common, ovarian cancer is associated with high morbidity and mortality. Both breast and ovarian cancer are associated with a family history of these conditions and, in some families, the pattern of cancers suggests the presence of a dominantly inherited cancer susceptibility gene. Two genes, *BRCA1* and *BRCA2*, have been identified as breast cancer susceptibility genes, and clinically significant mutations are estimated to occur in about 1 in 300 to 500 of the general population.

Objective: Screening for inherited breast and ovarian cancer susceptibility is a two-step process that includes an assessment of risk for clinically significant *BRCA* mutations followed by genetic testing of high-risk individuals. The evidence synthesis describes the strengths and limits of evidence about the effectiveness of selecting, testing, and managing patients in the course of screening in the primary care setting. Its objective is to determine the balance of benefits and adverse effects of screening based on available evidence. The target population includes adult women without preexisting breast or ovarian cancer presenting for routine care in the U.S.

Data Sources: Relevant papers were identified from multiple searches of MEDLINE® (1966 to October 1, 2004), Cochrane Library databases, reference lists of pertinent studies, reviews, editorials, and websites, and by consulting experts.

Study Selection: Investigators reviewed all abstracts identified by the searches and determined eligibility by applying inclusion and exclusion criteria specific to key questions about risk assessment, mutation testing, prevention interventions, and potential adverse effects including ethical, legal, and social implications (ELSI). Eligible studies had English-language abstracts, were applicable to U.S. clinical practice, and provided primary data relevant to key questions.

Data Extraction: All eligible studies were reviewed and data were extracted from each study, entered into evidence tables, and summarized by descriptive and statistical methods as appropriate. Two reviewers independently rated the quality of studies using USPSTF criteria.

Data Synthesis: A primary care approach to screening for *BRCA* genetic susceptibility for breast and ovarian cancer has not been tested. No studies directly evaluated whether screening by risk assessment and *BRCA* mutation testing leads to a reduction in the incidence of breast and ovarian cancer and cause-specific and/or all cause mortality. Assessment tools that estimate the risk of clinically significant *BRCA* mutations are available to clinicians, but have not been widely evaluated in primary care settings. Several referral guidelines have been developed for primary care, but there is no consensus or gold standard for use. Trials reported that genetic counseling may increase accuracy of risk perception, and decrease breast cancer worry and anxiety. Estimates of breast and ovarian cancer occurrence, based on studies of *BRCA* mutation prevalence and penetrance, can be stratified by family history risk groups that are applicable to screening. However, studies are heterogeneous and estimates based on them may not be reliable. Studies of potential adverse effects of risk assessment, genetic counseling, and testing reported decreased rather than increased distress. A meta-analysis of chemoprevention trials in women with unknown mutation status indicated statistically significant effects of selective estrogen

receptor modulators in preventing breast cancer and estrogen receptor-positive breast cancer, and significantly increased risks for thromboembolic events and endometrial cancer. Observational studies of prophylactic mastectomy and oophorectomy indicated reduced risks of breast and ovarian cancer in *BRCA* mutation carriers. Studies of patient satisfaction with surgery had mixed results; cancer distress improved, but self-esteem, body image, and other outcomes were adversely affected in some women. Applying this evidence to an outcomes table indicated that the numbers needed to screen to prevent one case of breast (4,000-13,000) or ovarian cancer (7,000) are high among women with an average risk of having a clinically significant *BRCA* mutation, and decrease as risk increases. Adverse effects also increase as more women are subjected to prevention therapies.

Conclusions: The evidence base for genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility as a screening strategy is limited by lack of studies demonstrating effectiveness, biases inherent in studies conducted in highly selected populations, and incomplete information on adverse effects.

Keywords: Genetic risk assessment, genetic testing, *BRCA1* and *BRCA2* mutations, breast cancer, ovarian cancer.

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Chapter 1. Introduction

Screening for inherited breast and ovarian cancer susceptibility is a two-step process that includes an assessment of risk for clinically significant *BRCA* mutations followed by genetic testing of high-risk individuals. The evidence synthesis describes the strengths and limits of evidence about the effectiveness of selecting, testing, and managing patients in the course of screening in the primary care setting. Its objective is to determine the balance of benefits and adverse effects of screening based on available evidence. The target population includes adult women without preexisting breast or ovarian cancer presenting for routine care in the U.S. The evidence synthesis emphasizes the patient's perspective in the choice of tests, interventions, outcome measures, and potential adverse effects and focuses on those that are available and easily interpreted in a clinical context. It also considers the generalizability of efficacy studies and interprets the use of the tests and interventions in community-based populations seeking primary health care.

Burden of Condition/Epidemiology

Breast cancer is the second most common cancer in women in the U.S. after nonmelanoma skin cancer, and is the second leading cause of cancer death after lung cancer.[1] In 2003, there were an estimated 211,300 new cases and 39,800 deaths from breast cancer.[1] The incidence of breast cancer increases with age[2] and is associated with several risk factors, although the majority of breast cancer occurs in women without known major risk factors.[2, 3]

Ovarian cancer is the fifth leading cause of cancer death among women in the U.S., accounting for an estimated 25,400 new cases and 14,300 deaths in 2003.[1] Risk for ovarian cancer also increases with age, peaking after age 80.[4] The 5-year relative survival rate for all stages of ovarian cancer in the U.S. is 50%, but may improve to 95% for women whose disease is detected and treated in early stages.[4] However, up to 75% of women with ovarian cancer have non-localized disease at the time of diagnosis because early stages are often asymptomatic. Five-year relative survival rates for women with regional and distant disease drop to 79% and 28%, respectively.[4]

Both 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 either a first-degree or a second-degree relative with breast cancer.[3, 5-8] In some families the pattern of cancers suggests the presence of a dominantly inherited cancer susceptibility gene. Two such genes identified to date are breast cancer susceptibility gene 1 (*BRCA1*) and breast cancer susceptibility gene 2 (*BRCA2*).[9, 10] Specific *BRCA* mutations (founder mutations) are clustered among certain ethnic groups such as Ashkenazi Jews,[11-13] and among families in the Netherlands,[14] Iceland,[15, 16] and Sweden.[17] Additional germ-line mutations associated with familial breast or ovarian cancer have been identified, and others are suspected.[18, 19] *BRCA1* and *BRCA2* mutations are also associated with increased risk of prostate cancer, and *BRCA2* mutations with increased risk of pancreatic and stomach cancers and melanoma.[20] Clinically significant, or deleterious, *BRCA1* and *BRCA2* mutations are mutations

that are associated or predicted to be associated with increased breast or ovarian cancer risk. Clinically significant mutations in either of the *BRCA* genes increase a woman's lifetime risk of breast cancer to 60% to 85%.[21, 22] Clinically significant *BRCA1* mutations increase ovarian cancer risk to 26%, and *BRCA2* mutations increase ovarian cancer risk to about 10%.[23-26] They are estimated to occur in 1 in 300 to 500 in the general population.[27-30]

Healthcare Interventions

Risk Assessment, Genetic Counseling, and Testing

Approaches to assessing personal risk for *BRCA* mutation status include models based on available data sets, checklists of criteria, pedigree analysis, knowledge of a deleterious mutation detected in a relative with cancer, and identification with groups known to have a higher prevalence of clinically significant *BRCA* mutations, such as the Ashkenazi Jewish population. Guidelines recommend testing for mutations only when an individual has personal or family history features suggestive of inherited cancer susceptibility, the test can be adequately interpreted, and results will aid in management.[31, 32] Risk status requires reevaluation when personal and/or family cancer history change. Several characteristics are associated with an increased likelihood of *BRCA* mutations.[33-36] These include breast cancer diagnosed at an early age, bilateral breast cancer, history of both breast and ovarian cancer, presence of breast cancer in one or more male family members, multiple cases of breast cancer in the family, both breast and ovarian cancer in the family, one or more family members with two primary cancers, and Ashkenazi Jewish background.

Genetic counseling is recommended prior to testing,[31] and is defined as a communication process that deals with the human problems associated with the occurrence, or the risk of occurrence, of a genetic disorder in a family.[37] A number of approaches are in practice, including educational, decision-making, and psychosocial support.[38] Providers of genetic counseling may be genetic counselors,[39-41] nurse educators,[42-44] or other professionals.[38]

The type of mutation analysis required depends on family history. A small number of clinically significant *BRCA1* and *BRCA2* mutations have been found repeatedly in different families, such as the three mutations common in the Ashkenazi Jewish population. However, most identified mutations have been found in only a few families.[45] Individuals from families with known mutations, or from ethnic groups with common mutations, can be tested specifically for them. Several clinical laboratories in the U.S. test for specific mutations or sequence specific exons (Table 1). The sensitivity and specificity of analytic techniques are determined by the laboratories and are not generally available. Prices range from $325 to $2,975 depending on the type of test.[46]

Individuals without linkages to families or groups with known mutations undergo direct DNA sequencing. In these cases, guidelines recommend that testing begin with a relative with known breast or ovarian cancer to determine if a clinically significant mutation is segregating in the family.[31] Myriad Genetic Laboratories provides direct DNA sequencing in the U.S. and reports analytic sensitivity and specificity both >99%.[46] Approximately 12% of high-risk families without a *BRCA1* or *BRCA2* coding-region mutation may have other clinically significant genomic rearrangements.[46, 47] Test results include not only positive (positive for a

deleterious mutation) and negative (no mutation detected) interpretations, but also variants of uncertain clinical significance which may comprise up to 13% of results.[33] A woman who has relatives with cancer and known deleterious mutations can be reassured about her inherited risk if her result is negative. However, a negative test result is less useful if her relatives have cancer but no detected deleterious mutations.

Ethical, Legal, and Social implications (ELSI)

Genetic testing is a relatively new technology in the field of disease prevention. Identifying and exploring ethical, legal, and social implications (ELSI) of genetic screening and testing is essential for ensuring safe and appropriate use of genetic information. ELSI topics cross disciplines of genetics, medicine, public health, ethics, law, and psychology, challenging practitioners to examine unfamiliar perspectives and information in making clinical decisions and recommendations. In screening for risk of inherited breast and ovarian cancer susceptibility, identification of ELSI is necessary for an accurate understanding of the scope of potential benefits and adverse effects.

Interventions to Reduce Risk

Interventions to reduce risk for cancer in *BRCA* mutation carriers include earlier, more frequent, or intensive cancer screening, chemoprevention, and prophylactic surgery. Screening for breast cancer in average-risk women includes mammograms every 1 to 2 years beginning at age 40.[48] A consensus panel of the Cancer Genetics Studies Consortium recommended that *BRCA* mutation carriers conduct monthly self-examinations beginning by age 18 to 21 years, annual or semiannual clinician examinations beginning at age 25 to 35 years, and annual mammography beginning at age 25 to 35 years.[49] Use of additional imaging modalities, such as magnetic resonance imaging (MRI) of the breasts,[50, 51] has also been suggested by experts because mammography is less accurate for premenopausal women with denser breast tissue.[52-55]

Currently, the U.S. Preventive Services Task Force (USPSTF) does not recommend screening average-risk women for ovarian cancer.[56] The consensus panel of the Cancer Genetics Studies Consortium advises *BRCA1* mutation carriers to undergo annual or semiannual screening using transvaginal ultrasound and CA-125 serum levels beginning at age 25 to 35 years.[49] Although *BRCA2* mutation carriers have less risk for ovarian cancer than *BRCA1* mutation carriers, the consensus panel suggests that they may elect this approach also.[49, 57]

Tamoxifen, a selective estrogen receptor modulator (SERM), was considered a candidate for chemoprevention of breast cancer based on its effectiveness in preventing recurrences in women with breast cancer.[58] Randomized controlled prevention trials support its use in preventing estrogen receptor-positive tumors in women with a family history of breast cancer.[59-63] Raloxifene, another SERM used primarily for treating osteoporosis, also reduced risk for breast cancer in one trial,[64] and studies of these and additional agents are ongoing.[65, 66] SERMs also have important adverse effects such as thromboembolism, endometrial cancer (tamoxifen), and vasomotor and other symptoms.[67, 68] The USPSTF currently recommends use of tamoxifen in women at increased risk for breast cancer and low risk for complications, and discourages its use in average-risk women.[69]

Prophylactic mastectomy and oophorectomy are also options for high-risk women, and the most recent studies focus on *BRCA* mutation carriers.[70-74] Bilateral total simple mastectomy with

or without reconstruction is currently the most common approach.[75, 76] This procedure provides more complete removal of breast tissue than the previously used subcutaneous mastectomy. However, no procedure completely removes all breast tissue,[77] and breast cancer can still occur postmastectomy.[78]

A National Institutes of Health (NIH) consensus conference in 1994 recommended that women with two or more first-degree relatives with ovarian cancer be offered prophylactic oophorectomy after completion of childbearing or at age 35 years, based on the mean age of ovarian cancer occurring in the mid to late 40s.[57] Surgical reports indicate the potential for ovarian cancer occurrence after bilateral oophorectomy, and some experts suggest undergoing bilateral salpingo-oophorectomy with hysterectomy to remove potential tumor sites.[79, 80] Despite this approach, the occurrence of peritoneal carcinomatosis remains a possibility.[81-83]

Analytic Framework and Key Questions

The patient population, interventions, health outcomes, and adverse effects of screening are summarized in an analytic framework (Figure 1). Corresponding key questions examine a chain of evidence about risk assessment for inherited cancer susceptibility in primary care settings, impact of genetic counseling, ability to predict cancer occurrence in women with average, moderate, and high family risks for deleterious mutations, and benefits and adverse effects of prevention interventions (Figure 2). In addition, ELSI studies related to specific key questions are included.

Chapter 2. Methods

Literature Search Strategy

Relevant papers were identified from multiple searches of MEDLINE® (1966 to October 1, 2004) and the Cochrane Library databases. Search strategies are described in Appendix A. Additional papers were obtained by reviewing reference lists of pertinent studies, reviews, editorials, and websites, and by consulting experts.

Inclusion/Exclusion Criteria

Investigators reviewed all abstracts identified by the searches and determined eligibility by applying inclusion and exclusion criteria specific to key questions (Appendix B). Full-text papers of included abstracts were then reviewed for relevance. Eligible studies had English-language abstracts, were applicable to U.S. clinical practice, and provided primary data relevant to key questions. 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 (e.g., retrospective or case-control studies).

Data Extraction and Synthesis

All eligible studies were reviewed and a "best evidence" approach was applied.[84] Data were extracted from each study, entered into evidence tables, and summarized by descriptive and statistical methods as appropriate. Two reviewers independently rated the quality of studies using criteria specific to different study designs developed by the USPSTF (Appendix C). When reviewers disagreed, a final rating was determined by reevaluations by the two initial reviewers and a third reviewer if needed.

Statistical Analysis

To estimate risks for breast and ovarian cancer due to clinically significant *BRCA* mutations, the screening population was stratified into groups at average, moderate, and high risk for carrying a mutation based on history of breast or ovarian cancer in first- and second-degree relatives. This approach allows use of published data that describe risks in similar terms. The following definitions were used:

- Average risk: No first-degree relatives and no more than one second-degree relative on each side of the family with breast or ovarian cancer.

- Moderate risk: One first-degree relative or two second-degree relatives on the same side of the family with breast or ovarian cancer.

- High risk: At least two first-degree relatives with breast or ovarian cancer.

Based on pooled data from over 100,000 women without breast cancer from 52 epidemiologic studies of familial breast cancer, approximately 93% of the screening population would be expected to be average risk, 7% moderate risk, and 0.4% high risk by these definitions.[85]

Ashkenazi Jewish women have higher risks for clinically significant *BRCA* mutations even if they have no affected first-degree relatives. In certain areas of the U.S., this group comprises an important proportion of women in primary care practices. For screening purposes, they were categorized in the following groups:

- Moderate risk: No first-degree relatives and no more than one second-degree relative on each side of the family with breast or ovarian cancer.

- High risk: At least one first-degree relative or two second-degree relatives on the same side of the family with breast or ovarian cancer.

Based on data from nearly 5,000 Jewish men and women living in the Washington, D.C., area of the U.S., approximately 79% of the screening population would be expected to be moderate risk, and 21% high risk by these definitions, although these estimates may vary regionally.[86]

Risks for developing breast and ovarian cancer in mutation carriers have been primarily calculated from families of women with existing breast and ovarian cancer. Determinations of risk in mutation carriers without these conditions are limited. To determine benefits and adverse effects of genetic testing in average-, moderate-, and high-risk groups, estimates of mutation prevalence as well as the probability of developing cancer given the presence of the mutation (penetrance) were determined for each risk group. Penetrance was calculated from data about the prevalence of *BRCA* mutations in women with and without breast and ovarian cancer, the probability of breast and ovarian cancer in the U.S. population estimated from SEER data[248] by using DevCan software,[87] and relative risks of breast and ovarian cancer in moderate- and high-risk groups.

For the meta-analysis of mutation prevalence for each risk group, the approach by DerSimonian and Laird was adopted,[88] where the logit of the prevalence and the corresponding standard errors were calculated for each study and used in the meta-analysis. The overall estimate of prevalence and its corresponding variance were then used to estimate penetrance. The meta-analysis of penetrance was based on Bayes' theorem and stratified by cancer type (breast or ovarian), risk group (average, moderate, and high), and age whenever data were available. Additional details of this method are provided in Appendix D.

A meta-analysis of chemoprevention trials was also performed to provide more precise estimates of effectiveness and adverse effects. All chemoprevention trials reported relative risk (RR) estimates, and the logarithm of the RR (logRR) and the corresponding standard errors were

calculated for each trial and used in the meta-analysis. The overall estimates of RR were obtained by using a random effects model.[88]

An outcomes table was developed to determine the magnitude of potential benefits and adverse effects of testing for *BRCA* mutations in the general population stratified by average, moderate, and high risk for a mutation based on family history as defined above. The number needed to treat (NNT) and number needed to screen (NNS) as well as other outcome variables were calculated from best estimates of assumption variables from published studies and results of analyses when available. Variation associated with these estimates was incorporated by using Monte Carlo simulations. The sampling distributions for estimates were either the underlying distribution on which calculation of the 95% confidence interval (CI) was based when available, or one that best approximated the point estimate and confidence interval. For example, if the assumption variable was penetrance, the logit of penetrance was approximately normally distributed and sampled, then transformed back to its original scale. For relative risk, the log of relative risk was approximately normally distributed. Risk reduction was calculated from the sampled log of relative risk. The point estimate and 95% confidence interval of NNT, NNS, and other outcome variables were based on 1,000,000 simulations.

Since there are no direct estimates of *BRCA* mutation prevalence for average- and moderate-risk groups, sensitivity analyses were conducted by assuming a range of prevalence values. Prevalence values were chosen such that when they were summed across the three risk groups, the total fell within the range for the general population (1 in 300 to 500).[30, 89] Calculations assumed that women are cancer free at age 20, and outcomes were calculated to age 40 years for breast cancer, age 50 years for ovarian cancer, and age 75 years for both because results at these ages were most often reported by studies. It was assumed that one-half of the mutations would be in *BRCA1* and one-half in *BRCA2,* and sensitivity analyses were also performed to determine whether this ratio (40/60, 50/50, 60/40) affects outcomes.

Size of Literature Reviewed

Investigators reviewed 2,211 abstracts identified by the searches (Appendix E), and excluded 1,380 articles from further review because they focused on excluded populations or did not address key questions. From the searches, 835 full-text articles were reviewed. An additional 279 non-duplicate articles identified from reference lists and experts were also reviewed.

Chapter 3. Results

Key Question 1. Does risk assessment and *BRCA* mutation testing lead to a reduction in the incidence of breast and ovarian cancer and cause-specific and/or all cause mortality?

Although several studies describe risk assessment methods that are relevant to primary care, none demonstrate that a screening approach enlisting risk assessment in a primary care setting followed by *BRCA* mutation testing and preventive interventions for appropriate candidates ultimately leads to a reduction in the incidence of breast and ovarian cancer and cause-specific and/or all cause mortality.

Key Question 2. What are the ethical, legal, and social implications of genetic screening for breast and ovarian cancer susceptibility?

A total of 229 studies of ethical, legal, and social implications (ELSI) of genetic screening were identified by the literature searches, reference lists, and experts. Studies pertinent to specific key questions are described in appropriate sections of this report (Key Questions 3b, 4, and 6).

Key Question 3a. How well does risk assessment for cancer susceptibility by a clinician in a primary care setting select candidates for *BRCA* mutation testing?

Determination of Family History

Family history of breast and ovarian cancer is the most important factor for determining risk for a deleterious *BRCA* mutation in a woman without cancer or known family mutation. For women with first-degree relatives with cancer, the relative risks for cancer have been estimated in meta-analyses as 2.1 (2.0-2.2) for breast cancer[8] and 3.1 (2.6-3.7) for ovarian cancer.[90] Decisions about referral, testing, and prevention interventions are often based on self-reports of family histories that include types of cancers, relationships within the family, and ages of onset. Appropriate decisions rely on family histories that are accurately reported by women and correctly obtained by clinicians.

The accuracy of family cancer history information was addressed in a systematic review of studies of validated self-reported family histories.[91] One study determined the sensitivity and specificity of a family history of breast or ovarian cancer in first-degree relatives reported by healthy individuals.[92] A report of breast cancer in a first-degree relative had a sensitivity of 82%, specificity of 91%, positive likelihood ratio of 8.9 (5.4-15.0), and a negative likelihood ratio of 0.20 (0.08-0.49).[92] A report of ovarian cancer in a first-degree relative was less reliable, and had a sensitivity of 50%, specificity of 99%, positive likelihood ratio of 34.0 (5.7-202.0), and a negative likelihood ratio of 0.51 (0.13-2.10).[92] Overall, accuracy was better in studies concerning first-degree rather than second-degree relatives.[91]

Tools to Assess Risk of *BRCA* Mutation

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.[93] Much of the data used to develop the models are from women with existing cancer. Models with potential clinical applications are described in Table 2.

Myriad Genetic Laboratories Models

Logistic regression models have been developed by the Myriad Genetic Laboratories,[34, 35, 94] a commercial laboratory in the U.S. providing DNA full sequence testing for *BRCA* mutations. One model predicts risk for *BRCA1* mutation and is based on a population of women with either early-onset breast cancer or ovarian cancer, or with a family history of breast or ovarian cancer.[35] This model also takes into account bilateral breast cancer, age of diagnosis, and Ashkenazi Jewish ancestry, and is not dependent on affected relatives. A second Myriad model predicts risk for both *BRCA1* and *BRCA2* mutations and is based on a population of women with breast cancer under age 50 or ovarian cancer who have at least one first- or second-degree relative with early breast or ovarian cancer.[34, 94] This model considers bilateral breast cancer, concurrent breast and ovarian cancer, and breast cancer under age 40.

Couch Model. The Couch Model is based on logistic regression of data from a population of women with breast cancer and a family history of breast and/or ovarian cancer, and predicts risk for *BRCA1* mutation.[36] Mutations were originally determined by conformation sensitive gel electrophoresis (CSGE) rather than DNA full sequencing, potentially underestimating mutation prevalence. A refined model now includes both *BRCA1* and *BRCA2* mutations using DNA full sequencing.[95] In this model, the individual may or may not have breast or ovarian cancer, but the family must have more than two cases of breast cancer. Predictors include the number of women diagnosed with breast cancer under age 50, concurrent breast and ovarian cancer, ovarian cancer, male breast cancer, and Ashkenazi Jewish ancestry.

***BRCA*PRO.** *BRCA*PRO is a Bayesian model providing estimates of risk for *BRCA1* and *BRCA2* mutations[96-98] that has been validated in populations of women with increased prevalence of specific mutations.[97, 99] The performance of *BRCA*PRO was compared with evaluations by cancer risk counselors in 148 pedigrees with women affected by breast or ovarian cancer who had *BRCA* mutation analysis. Using a greater than 10% *BRCA* gene mutation probability

threshold, the sensitivity for identifying mutation carriers was 94% for counselors and 92% for *BRCA*PRO, and specificity was 16% for counselors and 32% for *BRCA*PRO.[99] Studies are currently under way to evaluate *BRCA*PRO estimates compared with other models.[100] In *BRCA*PRO, the individual may or may not have breast or ovarian cancer, and it considers current age, age at diagnosis, bilateral breast cancer, concurrent breast and ovarian cancer, all first- and second-degree relatives with and without cancer, males with breast cancer, and Ashkenazi Jewish ancestry. It includes information on both affected and unaffected relatives. CancerGene is a user-friendly software program[101] that provides prior probabilities from *BRCA*PRO, but is much easier to use. A new version of Cyrillic software (Cyrillic 3) also includes *BRCA*PRO.[102]

Tyrer Model. This model integrates personal risk factors with a genetic analysis to provide a comprehensive risk estimate.[103] Personal risk factors include current age, age at menarche, parity, age at first childbirth, age at menopause, atypical hyperplasia, lobular carcinoma in situ, height, and body mass index (BMI). The individual may or may not have breast or ovarian cancer. Genetic analysis incorporates the high-risk, high-penetrance *BRCA1* and *BRCA2* germline mutations with the addition of a low-penetrance gene. This was created as a stand-in to account for the effect of all other unidentified genes. Methods include segregation analysis techniques based on Bayes' theorem. This model is accessible through a computer program that is not yet widely distributed, but available from the investigators.

Tools for Primary Care That Assess Risk and Guide Referral

The family history assessment tool (FHAT) was developed to assist clinicians in selecting patients for referral to genetic counseling.[104] The referral threshold was doubling of the general population lifetime risk for breast cancer or ovarian cancer (22%) as estimated by Claus[105] and *BRCA*PRO methods. With FHAT, points are assigned according to the number of relatives, third-degree relatives or closer, diagnosed with breast, ovarian, colon, or prostate cancer, and the relationship to the proband, age at diagnosis, and type and number of primary cancers. Patients with scores of 10 or more points warrant referral. Results of FHAT were compared with Claus and *BRCA*PRO estimates for 184 women with incident familial and non-familial breast cancer.[104] The sensitivity and specificity of FHAT for a clinically significant *BRCA1* or *BRCA2* mutation were 94% and 51%, respectively. This compares with sensitivity and specificity of 74% and 79% for a 20% threshold for having a clinically significant *BRCA1* or *BRCA2* mutation using *BRCA*PRO, and 74% and 54% using Claus.

The Manchester scoring system was developed in the U.K. to predict deleterious *BRCA1* or *BRCA2* mutations at the 10% likelihood level.[106] Points are assigned depending on type of cancer (breast, ovarian, pancreatic, or prostate), affected family members, and age at diagnosis and provide scores for *BRCA1* and *BRCA2* mutations separately. The scoring system was validated in three sample sets in other regions of the U.K. and compared with other existing models. The Manchester model (combined *BRCA1* and *BRCA2*) had 87% sensitivity and 66% specificity, comparing well with other models tested, including *BRCA*PRO with 61% sensitivity and 44% specificity.

Risk Assessment in Genetics (RAGs) is a computer program designed to support assessment and management of family breast and ovarian cancer in primary care settings.[107] It generates pedigrees after information about the proband and relatives are entered, categorizes risks of breast and ovarian cancer, generates referral guidelines based on the Claus model, and suggests

appropriate management. Scores from RAGs are based on family history of affected relatives and the age of the presenting patient. One of three risk levels is assigned: low (<10% risk of having a clinically significant *BRCA1* or *BRCA2* mutation), in which the patient is reassured and managed in primary care; moderate (10-25% risk), in which the patient is referred to a breast clinic; and high (>25% risk), in which the patient is referred to a clinical geneticist.[108] A study of a small random sample of general practitioners in the U.K. compared how well they managed 18 simulated cases using RAGs, Cyrillic, and pen and paper approaches.[109] RAGs resulted in significantly more appropriate management decisions and more accurate pedigrees, and was the preferred approach.[109] RAGs took 178 seconds (mean) to administer, which was longer than pen and paper but shorter than Cyrillic.[109]

Referral Guidelines

Referral guidelines have been developed by health maintenance organizations (HMOs),[110] professional organizations,[31, 32] cancer programs,[111, 112] state and national health programs,[113-116] and investigators[117] to assist primary care clinicians in identifying women at potentially increased risk for *BRCA* mutations (Table 3). Although specific items vary among the guidelines, most include questions about personal and family history of *BRCA* mutations, breast and ovarian cancer, age of diagnosis, bilateral breast cancer, and Ashkenazi Jewish heritage. Most guidelines are intended to lead to a referral for more extensive genetic evaluation and counseling, not directly to testing. There is currently no consensus or gold standard about the use of guidelines. The effectiveness of this approach has not been evaluated.

Key Question 3b. What are the benefits of genetic counseling prior to testing?

No studies describe cancer or mortality outcomes related to genetic counseling, although 10 randomized controlled trials reported psychological and behavioral outcomes (Appendix G). Of these, 4 met criteria for good quality[41, 118-120] and 6 for fair quality (Appendix H).[38-40, 42-44] Trials examined the impact of genetic counseling on breast cancer worry, anxiety, depression, perception of cancer risk, and intent to participate in genetic testing. Trials were conducted in highly selected samples of women, and results may not generalize to a screening population.

The trial most applicable to primary care practice randomized women at risk for clinically significant *BRCA* mutations to two groups and compared the effectiveness of a computer-based decision aid with standard genetic counseling.[120] The decision aid could potentially be used in primary care settings. Although knowledge scores increased in both groups, the decision aid was more effective than standard genetic counseling for increasing knowledge of breast cancer and genetic testing among women at low risk (<10% chance of deleterious *BRCA* mutation) ($p=0.03$), but not among women at high risk (≥10% chance). Perception of risk and intention to test were significantly lower for low-risk women using either method. The numbers of women undergoing mutation testing 1 month or 6 months after the intervention did not differ by type of intervention. Standard genetic counseling was more effective than the decision aid at reducing anxiety, although anxiety scores were within normal ranges for both groups at baseline and after either intervention.

Psychological Benefits

Results of nine trials indicated either decreased measures of psychological distress or no effect after genetic counseling (Table 4). Five of seven trials showed decreased breast cancer worry after genetic counseling,[38, 42-44, 119] and two showed no significant effect.[40, 118] Three studies reported decreased anxiety after genetic counseling,[38, 118, 120] and three reported no significant effect.[41, 43, 119] One study reported decreased depression after genetic counseling,[118] and four found no significant effect.[38, 41, 43, 119] These findings are consistent with a recent meta-analysis of 12 published studies on genetic counseling for breast cancer with randomized controlled trial or prospective study designs.[121] Results indicated that genetic counseling led to significant decreases in generalized anxiety (average weighted effect; $r = -0.17$, $p<0.01$), although the reduction in psychological distress was not significant ($r = -0.074$, $p<0.052$).

Perception of Cancer Risk

Women often overestimate their risk of breast cancer and/or deleterious *BRCA* mutations.[43, 89, 122] Most women responding to surveys, including those at average and moderate risk, report a strong desire for genetic testing[38, 123] even though only those at high risk would potentially benefit.

Five trials reported increased accuracy of cancer risk perception among women who received genetic counseling,[38, 40, 44, 119, 120] implying that genetic counseling may improve the predictive value of testing by reducing testing in moderate- or average-risk individuals. One study showed less accurate risk perception after genetic counseling, [118] and one had mixed results.[41] Three studies examining the intention to participate in genetic testing after counseling reported inconsistent results. One study indicated a decrease in intention,[39] another showed an increase in intention among African American, but not Caucasian women,[42] and the third study showed decreased intention among low-risk but not high-risk women.[120]

Key Question 3c. Among women with family histories predicting either an average, moderate, or high risk for a deleterious mutation, how well does *BRCA* mutation testing predict risk of breast and ovarian cancer?

Cancer risk in family history risk groups can be estimated by determining the prevalence of the mutation and its penetrance for breast and ovarian cancer for each risk group. A total of 38 studies of prevalence and penetrance were identified as relevant to this question (Appendixes I-L). These studies could not be rated for quality because their study designs are not addressed by the USPSTF criteria. Most studies used research laboratory techniques to detect clinically significant mutations that differ from the DNA sequencing available clinically. The prevalence of clinically significant mutations may be underestimated by one-third using these techniques.[124]

Prevalence

General Population

No direct measures of the prevalence of clinically significant *BRCA1* or *BRCA2* mutations in the general, non-Jewish U.S. population have been published. Models estimate it to be about 1 in 300 to 500.[27-30] For *BRCA1*, one model estimates a 0.12% prevalence rate.[25] The prevalence among those with a strong family history of cancer is estimated to be 8.7% based on one report of clinical referral populations that considered both *BRCA1* and *BRCA2* mutations together.[33] Additional prevalence estimates for individuals from referral populations with various levels of family history range from 3.4% (no breast cancer diagnosed in relatives younger than age 50, no ovarian cancer) to 15.5% (breast cancer diagnosed in a relative younger than age 50 and ovarian cancer diagnosed at any age).[46] Based on these estimates, the prevalence of *BRCA1* and *BRCA2* mutations in women at average risk could be considered as up to 0.24%, moderate risk from 0.24% to 3.4%, and high risk as 8.7% and above (Table 5). In the absence of direct measures, it can be assumed that one-half of the mutations would be in *BRCA1* and one-half in *BRCA2*.

Ashkenazi Jewish Population

For the Ashkenazi Jewish population unselected by family history, five studies provided data about prevalence of *BRCA1* mutations,[11, 12, 125-127] six for *BRCA2* mutations, [11, 12, 125-128] and four for mutations in the two genes combined.[11, 12, 125, 127] Results of the meta-analysis indicate an estimated prevalence of founder mutations of 1.9% (95% CI, 1.3%-2.8%), including 0.8% (0.5%-1.3%) *BRCA1* and 1.1% (0.9%-1.4%) *BRCA2* (Table 5).

For Ashkenazi Jews with a family history of breast or ovarian cancer, two studies provided prevalence data about *BRCA1* mutations,[11, 129] two for *BRCA2* mutations,[11, 129] and three for mutations in the two genes combined.[11, 33, 129] Results of the meta-analysis indicated an estimated prevalence of founder mutations of 10.2% (4.2%-22.9%) including 6.4% (1.1%-29.1%) *BRCA1* and 1.1% (0.6%-2.0%) *BRCA2* (Table 5).

Penetrance

Penetrance is the probability of developing breast or ovarian cancer among women who have a clinically significant *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.[21, 27, 28, 130-133] Among Ashkenazi Jewish women, penetrance estimates range from 26% to 81% for breast cancer and 10% to 46% for ovarian cancer.[11, 125, 134-138]

Limitations and Biases of Studies

Breast and ovarian cancer risk estimates are higher for relatives of women with breast cancer diagnosed at younger ages,[130] and for women from families with a greater number of affected relatives.[21, 131] Penetrance estimates are highest when based on data from families selected for breast or ovarian cancer—the selection approach used for genetic linkage studies and for clinical referrals. In addition to family history of cancer, penetrance may be influenced by the

mutation's location with the gene.[133, 139] Most studies do not have sufficient data to assess such heterogeneity.

For many published studies, penetrance was estimated from families without the benefit of genetic testing of all family members.[21, 27, 28, 130-135, 137] Studies used genetic segregation analysis in which the probability of having a clinically significant *BRCA1* and *BRCA2* mutation is estimated for each relative of an individual who has an identified mutation. Penetrance is estimated from the occurrence of breast or ovarian cancer and the *a priori* mutation carrier probability for each relative. Such estimates are typically based on family members of women who have breast or ovarian cancer (probands). Even when unselected for family history of breast and/or ovarian cancer, estimates from this study design can result in biased estimates of penetrance because the probands, and thus their family members, are more likely to have other risk factors for breast cancer that may affect penetrance.[140]

Many studies focus on women with existing breast and ovarian cancer, introducing bias, since breast or ovarian cancer survivors may have different mutation frequencies compared with women with newly diagnosed cancer. Also, mutations are underestimated by most research studies because they employ a 2-step process in testing. This involves an initial test to detect clinically significant mutations followed by direct DNA sequencing for positive specimens only, rather than complete DNA sequencing of all specimens.

Meta-analysis–General Population

The probabilities of having a mutation if breast or ovarian cancer is present were combined with mutation prevalence among women without cancer, and a range of estimates of breast and ovarian cancer risk in average-, moderate-, and high-risk groups to estimate penetrance in the general population. (Methods are described in Appendix D.)

Breast cancer penetrance. Nine studies provided data of the probability of a mutation if breast or ovarian cancer is present for women at average risk,[27, 29, 36, 132, 141-145] five studies for moderate risk,[27, 29, 142-144] and six for high risk.[28, 33, 36, 141, 144, 146] Breast cancer penetrance estimates to ages 40 and 75, respectively, for clinically significant *BRCA1* and *BRCA2* mutations were 8.5% (6.7%-10.6%) and 31.6% (20.4%-45.4%) in average-risk, 3.4% (2.0%-5.5%) and 19.0% (1.0%-32.6%) in moderate-risk, and 7.7% (6.5%-9.1%) and 59.1% (44.4%-72.3%) in high-risk groups (Table 6).

Ovarian cancer penetrance. Three studies provided data of the probability of having a mutation if breast or ovarian cancer is present for women at average risk,[133, 147, 148] three for moderate risk,[133, 144, 147] and three for high risk.[33, 141, 149] Ovarian cancer penetrance estimates to ages 50 and 75 were 13.0% (9.6%-17.4%) and 19.3% (13.7%-26.4%) in average-risk, no data for age 50 and 18.6% (14.0%-24.3%) in moderate-risk, and 4.0% (3.1%-5.2%) and 15.6% (12.9%-18.9%) in high-risk groups (Table 7).

These penetrance estimates are similar to those published for a combined analysis of 22 studies based on case series data from women unselected for cancer family history.[130] Breast and ovarian cancer risk estimates to age 70 years for women who have a *BRCA1* mutation were 65% (44%-78%) and 39% (18%-54%), respectively; for *BRCA2* mutation carriers, estimated breast and ovarian cancer risks were 45% (31%-56%) and 11% (2%-19%), respectively.

Meta-analysis–Ashkenazi Jewish Population

Breast cancer penetrance. Ten studies provided data of the probability of having a mutation if breast or ovarian cancer is present for Ashkenazi Jewish women without a family history,[86, 125, 134, 137, 138, 144, 150-153] and nine for those with a family history.[33, 86, 125, 128, 134, 150-153] Among Ashkenazi Jewish women without a family history of breast or ovarian cancer, penetrance estimates to ages 40 and 75 were 5.0% (3.0%-8.3%) and 33.7% (24.1%-44.9%) (Table 6). For those with a family history, penetrance estimates to ages 40 and 75 were 4.9% (1.9%-12.0%) and 34.7% (17.6%-57.0%) (Table 6).

Ovarian cancer penetrance. Five studies provided data to determine ovarian cancer penetrance for women without a family history,[127, 133, 135, 152, 154] and two for those with a family history.[33, 135] Among Ashkenazi Jewish women without a family history of breast or ovarian cancer, penetrance estimates to ages 50 and 75 were 7.5% (4.9%-11.3%) and 21.4% (14.9%-29.7%) (Table 7). For those with family history, penetrance estimates to ages 50 and 75 were 3.3% (1.3%-7.9%) and 18.1% (7.6%-37.3%) (Table 7). These penetrance estimates are consistent with those published in individual studies of Ashkenazi Jewish women.

Key Question 4. What are the adverse effects of risk assessment, counseling, and testing?

Adverse effects of risk assessment, including genetic counseling, and testing include the potential for false positive and false negative results at each step of the process leading to false reassurance or inappropriate interventions. No studies directly addressed these issues. However, several studies described potential emotional distress.

A total of 57 studies, including 10 randomized controlled trials and 47 observational studies, were identified as relevant. Of these, 40 studies using non-standardized measures were excluded from further analysis. Nine fair to good quality studies assessing emotional distress were included (Appendixes M and N), and results are summarized in Table 8.[155-163] Eight poor-quality studies were excluded because of high or differential loss to follow-up, attrition, contamination, failure to consider important outcomes, lack of adjustment for potential confounders, or poorly defined interventions.[164-171]

One randomized controlled trial[156] and eight observational trials with pre-post,[163] case series,[155] longitudinal,[160] prospective cohort,[157, 159, 161, 162] and non-comparative[158] designs assessed breast cancer risk assessment, genetic testing, or both and their subsequent impact on distress measured as breast cancer worry, anxiety, or depression. All studies included genetic counseling. Studies varied in the number of distress indicators reported. Follow-up periods also varied; the first follow-up was defined as immediate to 2 weeks in three studies,[155, 156, 162] 4 weeks in four studies,[157, 159, 160, 163] and 4 months in one study.[161] Final follow-up was defined as 6 months for all studies but two.[158, 161]

Overall, more studies showed decreased rather than increased distress indicators after risk assessment and testing (Table 8). However, generalizability is limited, and only two studies distinguished between mutation carriers and non-carriers.[159, 161]

Breast Cancer Worry

Two studies reported decreased breast cancer worry at the first follow-up evaluation,[156, 157] and one at both the first and final evaluations.[157] These studies included women from high-risk breast cancer families,[156] and a mixed group of women at average and high risk who tested negative for *BRCA* mutations.[157] One study of women from high-risk breast cancer families showed increased breast cancer worry at first follow-up but had no additional follow-up data.[160] Increased breast cancer worry for mutation carriers[161] was seen at the final follow-up (12 months) in one study .[161]

Anxiety

One study reported decreased anxiety for mutation carriers at the final 12-month follow-up evaluation, and decreased anxiety at the first 4-month follow-up for non-mutation carriers.[161] A study of women in the largest known kindred identified with a deleterious *BRCA1* mutation showed increased anxiety 1 to 2 weeks after testing, especially in carrier women who were tested first in their families and whose tested siblings were non-carriers.[162] In contrast, three other studies of women with a family history of breast cancer,[157, 160, 163] including women from high-risk families,[160] showed decreased anxiety at the first 1-month follow-up evaluation, and one showed continued decreased anxiety at 6-month evaluation[157]

Depression

Three studies with depression outcomes showed mixed results. Members of extended hereditary breast or ovarian cancer families, 27 with deleterious *BRCA1* mutations and 6 with deleterious *BRCA2* mutations, reported an increase in depression at the first and final follow-up evaluations for those who had cancer-related stress symptoms and declined testing, and a decrease in depression among non-carriers who were tested.[159] Another study of women with family histories of breast or ovarian cancer showed decreased depression in non-carriers at the first 4-month follow-up.[161] A study of women from high-risk families that did not distinguish impact on carriers vs. non-carriers found a decrease in depression after the first 1-month follow-up.[160]

Differential Impact of Risk Assessment, Testing, or Both on Distress

Distress varied by whether studies evaluated risk assessment, genetic testing, or both. When risk assessment was evaluated in four studies, one showed an increase in breast cancer worry.[160] There were no increases in other distress measures,[156, 158, 163]but decreases in breast cancer worry,[156] anxiety,[160, 163] and depression.[160]

When genetic testing was evaluated in three studies,[155,159,162] results indicated no increased breast cancer worry, but in one study results indicated increased anxiety at the first follow-up evaluation [162] A study evaluating carriers and non-carriers showed increased depression at the first and final follow-up evaluations for those with high cancer-related stress who declined testing, and decreased depression for non-carriers who were tested.[159]

In the two studies including both risk assessment and genetic testing, results were mixed. One study showed increased breast cancer worry at both follow-up evaluations for mutation

carriers,[161] while the other, which evaluated only those who tested negative, showed decreased breast cancer worry.[157] The first study showed decreased anxiety at the first follow-up for non-carriers and at the final follow-up for mutation carriers. It also showed decreased depression at the first follow-up for non-carriers.[161] The second study showed decreased anxiety at first and final follow-up, and did not assess depression.[157]

Key Question 5. How well do interventions reduce the incidence and mortality of breast and ovarian cancer in women identified as high-risk by history, positive genetic test results, or both?

Intensive Screening

Breast Cancer

Intensive screening for breast cancer in *BRCA* mutation carriers is recommended by expert groups,[172] and is based on favorable results of programs designed for women with familial risk (Table 9).[55, 173-181] However, there are no trials of the effectiveness of intensive screening for *BRCA* mutation carriers in reducing mortality. Recent descriptive studies report increased risks for interval cancers (those occurring between mammograms) in *BRCA* mutation carriers with and without prior cancer undergoing annual mammographic screening.[70, 173, 182, 183] These data imply that yearly mammograms may miss highly proliferate cancers that are more common in *BRCA* mutation carriers.[184-186]

In one study, high-risk women, including 113 *BRCA1* and 15 *BRCA2* mutation carriers without prior breast cancer, were followed in an intensive screening program at a family cancer clinic in the Netherlands that included monthly breast self-examination, twice-yearly clinical breast examinations, yearly mammography with MRI for those with dense breast tissue and/or *BRCA* gene mutations, and ultrasonography and fine-needle biopsy when indicated.[173] Sensitivity of this approach for detecting breast cancer was 74% overall, but dropped to 56% for *BRCA* mutation carriers, and four of the nine breast cancer cases among mutation carriers were detected during the period between mammograms (44%).[173]

Additional studies of *BRCA* mutation carriers, including both women with and without previous breast cancer diagnoses, enrolled in similar programs also report high proportions of interval cancers. Four of 13 mutation carriers undergoing intensive screening at the Columbia-Presbyterian Comprehensive Breast Center in New York had breast cancer detected at the time of their annual mammograms, and 6 women had interval malignancies that presented as palpable masses from 2 to 9 months (mean 5 months) after the last mammogram (60%).[182] A prospective study of *BRCA* carriers undergoing either preventive surgery or intensive screening reported that 6 of 12 mutation carriers who developed breast cancer while undergoing intensive screening were interval cases (50%).[183]

To improve detection of early breast cancer in *BRCA* mutation carriers, a comparison of four intensive screening modalities was conducted in 236 Canadian women with *BRCA1* or *BRCA2* mutations aged 25 to 65.[55] Women underwent one to three annual screening examinations

including MRI, mammography, and ultrasound with clinical breast examinations provided every 6 months. MRI was more sensitive for detecting breast cancers (sensitivity 77%, specificity 95.4%) than mammography (sensitivity 36%, specificity 99.8%), ultrasound (sensitivity 33%, specificity 96%), or clinical breast examination alone (sensitivity 9%, specificity 99.3%). Use of MRI, ultrasound, and mammography together had a sensitivity of 95%. Only one interval cancer was reported, and 14% of women had a biopsy that proved to be benign. MRI has advantages over mammography for detecting lesions in denser breast tissue and *BRCA1*-related cancers that have morphologic features suggesting a more benign mammographic image.

Ovarian Cancer

Data are limited regarding benefits of intensive screening strategies for ovarian cancer in *BRCA* mutation carriers. One study using transvaginal ultrasound to screen 1,610 women with a family history of ovarian cancer found 3.8% abnormal scans, and only 3 of 61 women with abnormal scans had ovarian cancer.[187]

Chemoprevention

Selective Estrogen Receptor Modulators (SERMs)

Four randomized placebo-controlled prevention trials of tamoxifen, three rated fair to good quality[59-61] and one rated fair quality,[62] and one good quality trial of raloxifene[64] with breast cancer incidence and mortality outcomes have been published (Appendixes O and P), and a trial comparing these agents is in progress.[65, 188] None of the trials specifically evaluated chemoprevention for women with *BRCA* mutations, although a genomic analysis of women developing breast cancer in one tamoxifen trial has been published.[189] No trials of chemoprevention using SERMs for ovarian cancer have been published. All trials reported high loss to follow-up (60% to 96% at 60 months), and three trials reported more loss from treatment than placebo groups due to side effects.[59, 61, 64]

Three tamoxifen trials had inclusion criteria based on assessment of risk for breast cancer, including the Royal Marsden Hospital Trial, International Breast Cancer Intervention Study (IBIS-I), and National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial P-1 (BCPT P-1) (described in Appendix O).[59-61] Two other trials did not assess subjects for breast cancer risk, and women in these studies could have lower risks of breast cancer than the general population. The Italian Tamoxifen Prevention Study included women who had had hysterectomies for benign conditions, with nearly half reporting previous bilateral oophorectomies, potentially reducing their risks for breast cancer.[62] The Multiple Outcomes of Raloxifene Evaluation (MORE) study was primarily a fracture prevention trial that evaluated breast cancer as a secondary outcome, and included postmenopausal women with osteoporosis.[64] Osteoporosis may be a marker for non-use of postmenopausal hormone therapy and low endogenous estrogen production lowering risk for breast cancer.[190, 191]

All trials enrolled healthy women without previous breast cancer; measured incident breast cancer cases and deaths; were multicenter, double-blind, and placebo controlled; and used the same dose of tamoxifen (20 mg per day), except for MORE, which used raloxifene (60 or 120 mg per day). The smallest trial enrolled approximately 1,200 women in each arm of the study,[61] and the largest enrolled over 6,500 in each arm.[60] Mean follow-up ranged from 40 months in

MORE to 70 months in the Royal Marsden Hospital Trial. Estrogen use during the study varied from 40% of women in IBIS-I, 26% in the Royal Marsden Hospital Trial, 14% in the Italian Tamoxifen Prevention Study, to 10% or less in the BCPT P-1 and MORE. Data were not provided to distinguish what proportion of estrogen users were using progestin as well.

For the two largest trials, tamoxifen significantly reduced the overall risk for breast cancer (Table 10).[59, 60] Tamoxifen reduced risk for users in all age groups, and reduced estrogen receptor-positive but not estrogen receptor-negative tumors.[59, 60] The Royal Marsden Hospital Trial and Italian Tamoxifen Prevention Study reported nonstatistically significant reductions in risk.[61, 62] The MORE trial reported significant reductions in risk among raloxifene users at both the 60 and 120 mg per day doses for total cases as well as invasive and estrogen receptor-positive cases (Table 10).[64] These results persisted with an additional year of treatment and follow-up.[192]

Combining all trials in a meta-analysis resulted in a relative risk for total breast cancer of 0.62 (0.46-0.83) (Figure 3). Results were similar when including only the three tamoxifen trials that used family history of breast cancer as inclusion criteria, and when including the four tamoxifen trials only (Figure 3). Few deaths from breast cancer were reported in all the trials, and there were no differences between treatment and placebo groups. The relative risk was further reduced for estrogen receptor-positive breast cancer (4 trials; 0.39; 0.20-0.79) (Figure 4).

Treatment effects of tamoxifen could vary depending on the type of mutation. *BRCA* mutation status was determined in some women who developed breast cancer in BCPT P-1. Genomic analysis of 288 women indicated[189] 6 of 7 cases with *BRCA1* mutations were estrogen receptor-negative (86%), and 6 of 9 cases with *BRCA2* mutations were estrogen receptor-positive (67%), consistent with known distributions.[189] The point estimate for breast cancer for *BRCA2*, but not *BRCA1,* carriers using tamoxifen approximated that of the total population of tamoxifen users for estrogen receptor-positive tumors (RR 0.31; 0.22-0.45).[189]

Oral Contraceptives

No randomized controlled trials of oral contraceptives to prevent breast or ovarian cancer have been published. Observational studies indicate associations between oral contraceptives and reduced ovarian cancer in the general population[193-195] as well as *BRCA* mutation carriers,[196] but increased breast cancer among women with family histories of breast cancer.[197]

Breast cancer. A retrospective cohort study of families of breast cancer probands diagnosed between 1944 and 1952 at the University of Minnesota collected follow-up data on families 40 years later.[197] Use of oral contraceptives was associated with a significantly increased risk of breast cancer among sisters and daughters of the probands (RR 3.3; 1.6-6.7), but not among granddaughters and nieces or non-blood relatives.[197] Risk was highest for women using oral contraceptives prior to 1975, when higher dosages of estrogen and progestins were used. Small numbers of cases using oral contraceptives after 1975 and younger ages of granddaughters restrict these estimates.

A small study of women with breast cancer compared past oral contraceptive use of mutation carriers with non-carriers.[198] Results indicated that more mutation carriers than non-carriers used oral contraceptives for more than 48 months before a first full-term pregnancy (OR 7.8; 1.1-55.0).[198]

Ovarian cancer. A case-control study of *BRCA* mutation carriers with ovarian cancer and their sisters without ovarian cancer (both mutation carriers and non-carriers) indicated reduced risk among those with any past use of oral contraceptives (OR 0.5; 0.3-0.8).[196] Risk decreased with increasing duration of use and was protective for carriers of either *BRCA1* or *BRCA2* mutations.[196] A population-based case-control study of ovarian cancer among *BRCA1* and *BRCA2* mutation carriers among Jewish women in Israel indicated that risk of ovarian cancer decreased with each birth, but not with increased duration of oral contraceptives.[127] A study of risk factors for ovarian cancer included *BRCA1* mutation carriers and non-carriers with ovarian cancer identified through registries compared with matched controls identified randomly in the San Francisco Bay Area.[199] Results indicated associations between reduced risk for ovarian cancer and ever use of oral contraceptives, duration of oral contraceptive use, history of tubal ligation, and increasing parity. Risk reduction was similar between mutation carriers and non-carriers. Differences between results of studies may be due to discrepancies in populations, methods, and confounders, or chance and other factors.

Prophylactic Surgery

No randomized controlled trials of prophylactic surgery have been conducted, and investigators acknowledge that this approach would not be ethical. Cohort studies of prophylactic surgery present several methodologic limitations to consider when interpreting their results.[200]

Biases Leading to Overestimation of Effect

For subjects selecting surgery, the course of events leading to surgery progresses in a sequence that can be easily captured in cohort studies, i.e., women obtain test results, make a decision about surgery, and then undergo the procedure. This course of events is less clear for women in nonsurgical comparison groups, particularly if they are not enrolled prospectively. Many of these women underwent testing after receiving a diagnosis of cancer. Risk reduction from surgery would be overestimated because the comparison group would be weighted with women with cancer.

This bias may be even more pronounced in studies enrolling women who are related to each other.[70, 72] A woman with cancer who then undergoes testing may be selected for the nonsurgical comparison group. In the meantime, she may have influenced her sister without cancer to undergo testing and surgery and become part of the intervention group. Subjects in the comparison group should be free of cancer at the point of follow-up in order to establish a similar baseline risk for both surgical and nonsurgical groups.

Women who choose prophylactic mastectomy may be more likely to also choose prophylactic oophorectomy[70, 74] and experience a cumulative reduction in risk for breast cancer that would be attributed to only the mastectomy. Prophylactic oophorectomy may act as both a confounder and an effect modifier for breast cancer.

Parity and young age at first birth are associated with decreased breast and ovarian cancer risk, and women who experienced childbirth at early ages and multiple times may have more benefit from prophylactic oophorectomy.[72] Parous mutation carriers may be more likely to elect prophylactic oophorectomy and at younger ages than nonparous women. This could lead to an

overestimate of effect. Similarly, other important confounders should also be considered, such as increased use of hormone therapy in women undergoing oophorectomy.[72, 73]

Biases Leading to Underestimation of Effect

Selection of comparison groups is problematic because even if subjects are well matched on type of mutation, age, and other factors, it is currently not possible to match unrelated subjects on expected penetrance. Penetrance varies widely, and members of families with more cases of cancer, and likely higher prevalence and higher risk than the comparison group, may be more likely to choose prophylactic surgery for themselves.

Prophylactic surgery may reveal clinically undetected tumors. Studies that include this event in the surgery group could underestimate the efficacy of surgery for incidence outcomes, and overestimate it for mortality outcomes. Excluding these tumors entirely, however, would bias survival outcomes because the surgery may have increased life expectancy.

The type of prophylactic procedure could also influence outcomes. Patients undergoing mastectomy at times when subcutaneous mastectomies were performed, rather than total mastectomies, may have higher subsequent breast cancer rates because more residual breast cancer tissue remained after surgery than women undergoing total mastectomy. Most of the women in a retrospective study at the Mayo Clinic had subcutaneous mastectomies.[201] Similarly, results from an oophorectomy could be less optimal than from a salpingo-oophorectomy or salpingo-oophorectomy with hysterectomy because of residual tissue at continued risk for cancer.

Bilateral Mastectomy

Four studies of prophylactic bilateral mastectomy in high-risk women have been published, including two retrospective cohort studies based on medical records at the Mayo Clinic,[201, 202] a prospective cohort study of mutation carriers in the Netherlands,[70] and a study of mutation carriers with prospective and retrospective cohort data from multiple centers in North America and Europe[71] (Appendix Q). Studies of mutation carriers ranged from 26 to 483 subjects and follow-up for 3 to 14 mean years postmastectomy. Study quality was fair for two studies,[70, 202] and two studies had designs that did not fit USPSTF criteria (Appendix R).[71, 201]

Study results were consistent, indicating an 85% to 100% risk reduction for breast cancer, despite differences in study designs and comparison groups ranging from sisters,[201] matched controls,[71] a surveillance group,[70] and penetrance models.[202]

Bilateral Oophorectomy

Four studies of prophylactic oophorectomy met inclusion criteria, including a retrospective study of families with members with breast and ovarian cancer,[203] two retrospective cohort studies of mutation carriers undergoing oophorectomy compared with matched comparison groups in North America and Europe,[72, 73] and a prospective cohort study of mutation carriers undergoing elective oophorectomy or surveillance[74] (Appendix Q). Average follow-up time in the retrospective studies was from 5 to 11 years and in the prospective study 2 years. Study quality was fair for the prospective study[74] and the retrospective study of family members,[203] and two studies had designs that did not fit USPSTF criteria (Appendix R).[72, 73]

All studies reported reduced risks for ovarian and breast cancer with prophylactic oophorectomy, although numbers of cases were small and the confidence intervals for the only prospective study crossed 1.0 for both outcomes.[74] Overall, the risk reduction for ovarian cancer ranged from 85% to 100%, and for breast cancer from 53% to 68%. One study found that oophorectomy after the age of 50 years was not associated with substantial breast cancer risk reduction,[72] consistent with other studies of oophorectomy in the general population.[204-207]

Tubal Ligation

Tubal ligation has been associated with a decreased risk of invasive epithelial ovarian cancer in observational studies.[194, 208, 209] A matched case-control study of mutation carriers with and without ovarian cancer indicated a reduced odds ratio among controls who underwent previous tubal ligation when adjusted for oral contraceptive use, parity, history of breast cancer, and ethnic group (OR 0.39; 0.22-0.70).[210] This protective effect was present only among *BRCA1* mutation carriers, although the number of *BRCA2* carriers was small in this study.

Key Question 6. What are the adverse effects of interventions?

Intensive Screening

No studies were identified that describe the adverse effects of intensive screening for breast or ovarian cancer. Potential adverse effects include inconvenience of frequent examinations and procedures, exposure to ionizing radiation that could increase risk for breast cancer,[211] cost, harms resulting from false positive findings and subsequent testing and biopsies, and false reassurance for women who may have increased risks for developing cancer between periodic screening tests.

Chemoprevention

Several adverse effects were reported in the tamoxifen and raloxifene trials (Table 11). All trials indicated increased risk for thromboembolic events, including pulmonary embolism and deep vein thrombosis (5 trials; 2.21; 1.63-2.98; Figure 5).[59-62, 64] Three tamoxifen trials reported increased incidence of stroke, although there were few cases and the confidence intervals crossed 1.0 (1.50; 1.01-2.24; Figure 6).[59, 60, 62] Three tamoxifen trials reported increased endometrial cancer (2.42; 1.46-4.03; Figure 7).[59-61] All cause death was significantly increased for tamoxifen users in IBIS-I only (2.27; 1.12-4.60) (Figure 8).[59]

Significantly more women in the tamoxifen group of the BCPT P-1 study developed cataracts during the course of the study than women in the placebo group (RR 1.14; 1.01-1.29).[60] This finding was not reported in the other trials. Tamoxifen trials reported significantly increased hot flashes,[59-61] vaginal discharge, bleeding, and other gynecologic problems,[59-61] brittle nails,[59] and mood changes.[61]

A report on quality of life indicators from the BCPT P-1 study indicated increased vasomotor

symptoms (hot flashes, cold sweats, night sweats), increased gynecologic symptoms (vaginal discharge, itching), and relatively small (<4%) but consistent differences in three domains of sexual functioning (decreased sexual interest, arousal, and orgasm) in the tamoxifen group.[212] There were no differences between groups on measures of mental health including depression.[212]

Adverse effects reported in the MORE trial by at least 2% of each raloxifene group and more frequently than the placebo group included flu syndrome (13%), hot flashes (10% to 12%), leg cramps (7%), endometrial cavity fluid (8% to 9%), and peripheral edema (5% to 7%).[64, 192]

Prophylactic Surgery

Mastectomy

Little information exists about the complications of prophylactic mastectomy in healthy high-risk women, and data from breast cancer patients may not be generalizable. In a series of 112 high-risk women (79 mutation carriers) who had prophylactic mastectomies with immediate reconstruction, 21% had complications including hematoma, infection, contracture, or implant rupture.[213] Use of autologous tissue may eliminate the need for silicone implants but may result in higher complication rates.[71]

Oophorectomy

Surgical complications attributable to prophylactic oophorectomy are not well described and may vary with the type of surgical technique (laparotomy versus laparoscopy).[214] A study of operative techniques used for 180,000 hysterectomies in 180 hospitals in the U.S. indicated an incidence of less than 3% for complications such as infection, bleeding, and urinary tract and bowel injury.[215] Only one study of prophylactic oophorectomy in *BRCA* mutation carriers reported surgical complications.[74] In this study, 4 of 80 women experienced complications including wound infection, perforation of the bladder, distal obstruction of the small bowel attributed to adhesions, and perforation of the uterus.[74]

Premenopausal high-risk women are not only the most likely to benefit from prophylactic oophorectomy, but are also the most likely to experience side effects from the surgery, including loss of fertility. Induction of premature menopause with associated symptoms of hot flashes, vaginal dryness, sexual dysfunction, sleep disturbances, and other symptoms, as well as increased osteoporosis, need to be considered. Use of postmenopausal hormone therapy can relieve symptoms[216] and protect against osteoporotic fractures,[217] but may also increase risk for breast cancer,[218] although use of estrogen without progestin may prove less harmful.[219] Lack of data for *BRCA* mutation carriers specifically complicates these management decisions.[220, 221]

Psychosocial Impact

Few descriptive studies of the psychosocial impact of prophylactic mastectomy or oophorectomy on high-risk patients have been published. Patient surveys indicate that although 57% of women at high risk for breast cancer consider prophylactic mastectomy an option,[222] only 16% to 20% rate it as a favorable option,[223, 224] and only 9% to 17% of women actually proceed with the surgery.[222, 224, 225]

The largest study of patient impact evaluated patients' long-term satisfaction and

psychological and social function following prophylactic mastectomy at the Mayo Clinic after mean follow-up of 14.5 years.[226] Overall, 70% of women were satisfied with the procedure, 11% neutral, and 19% dissatisfied. A majority (74%) reported diminished levels of emotional concern about developing breast cancer after mastectomy. Substantial minorities of women reported dissatisfaction with body appearance (36%), feelings of femininity (25%), sexual relationships (23%), self-esteem (18%), level of stress (14%), and emotional stability (9%).[226]

A study using a prophylactic mastectomy registry consisting of a volunteer population with mean follow-up of nearly 15 years postmastectomy indicated that 5% expressed regrets about the procedure.[227] The only significant factor distinguishing those with regrets from those without was that the discussion concerning prophylactic mastectomy was initiated by their physicians rather than by themselves ($p<0.05$).[227] In this study, 90% of those who were unhappy with their surgery had no preoperative psychological counseling.[227]

A prospective study of psychological morbidity of patients choosing to undergo prophylactic mastectomy and those of similar risk declining mastectomy administered six questionnaires preoperatively and again 6 and 18 months postoperatively.[228] Although both groups had similar levels of distress at baseline, distress decreased significantly over time for women undergoing surgery (58% preoperative; 41% at 6 months, $p=0.04$; 29% at 18 months, $p<0.001$), but not for women declining surgery (57% preoperative; 43% at 6 months, $p=0.08$; 41% at 18 months, $p=0.11$).[228]

In another small study of women at increased risk for breast cancer because of family history, women selecting surgery reported more breast cancer worry, had higher estimated risk, and more previous breast biopsies than those declining.[222] Women completing surgery were satisfied with their decision, although satisfaction with reconstruction was mixed.[222]

A prospective study on the impact of oophorectomy on women without cancer but with a strong family history of breast and/or ovarian cancer showed that prophylactic oophorectomy reduced anxiety about ovarian cancer ($p=0.029$).[229] Most (86.4%) of the 22 women who had the procedure reported a high degree of satisfaction with their decision at 3-year follow-up.[229] Other studies of the effects of oophorectomy in the general population focus on sexuality, mood, and menopausal symptoms and are inconclusive.[230-232] A small retrospective study of high-risk women compared psychosocial outcomes of women undergoing prophylactic oophorectomy with those undergoing intensive screening.[233] Women undergoing oophorectomy had significantly poorer scores on the role-emotional and social functioning scales of the Short Form-36 Health Status Questionnaire, and reported more menopausal symptoms on the General Health Questionnaire. There were no significant differences between groups for cancer worry or sexual functioning.[233]

Outcomes Table

A summary of the evidence, including the level and quality of evidence, for each key question addressed in the evidence synthesis is provided in Table 12. No trials of screening for *BRCA* mutations in the general population that provide direct measures of benefits and adverse effects are available. In the absence of such trials, synthesis of data from indirect evidence can provide estimates. An outcomes table was developed to determine the magnitude of potential benefits and adverse effects of screening for *BRCA* mutations in the general population stratified

by average, moderate, and high risk for mutations according to family history as previously defined. A summary of the assumptions and outcomes for the general population is provided in Table 13, and additional outcomes tables with sensitivity analyses are in Appendix S. Each assumption is associated with uncertainties and ranges of potential estimates that may not be fully considered in calculating the outcomes.

Estimates of the prevalence of *BRCA1* and *BRCA2* mutations were based on best estimates from published studies and results of the meta-analysis when multiple studies were available (Table 5). For the average- and moderate-risk groups, ranges of prevalence rates were used to represent a range of risk. Estimates of the penetrance of breast and ovarian cancer in those with clinically significant mutations were based on results of the meta-analysis of published studies (Tables 6 and 7). An estimate of risk reduction by using chemoprophylaxis with SERMs was obtained from the meta-analysis of chemoprevention trials (Figure 3). Estimates of risk reduction from preventive mastectomy or oophorectomy surgeries were obtained from studies determined to be of the highest quality.[70, 74] Risks of complications from drugs or surgeries were determined from the same studies as the treatment effects. Estimates of the proportion of candidates choosing SERMs, mastectomy, or oophorectomy were based on surveys of patient preferences and compliance during clinical trials and were discussed with experts.[222, 224, 225] Calculations assumed that women are cancer free at age 20, and outcomes were calculated to age 40/50 and age 75 years.

Results for the general population are summarized in Table 13 and Figures 9 and 10. These estimates assume prevalence rates of mutations of 0.12% for average-risk, 1.5% for moderate-risk, and 8.7% for high-risk women. This combination of prevalence rates reflects an overall population mutation rate of 1 in 397. The NNS to prevent one case of breast cancer in a hypothetical cohort of 100,000 women is dependent on which prevention therapy is chosen. For women with average risk, the NNS to prevent one case of breast cancer by the age of 75 years by using a SERM is 12,862 (5,425-64,048), for mastectomy 11,049 (6,243-27,037), and for oophorectomy 4,100 (1,985-255,926). Approximately 7,072 (3,610-584,750) women with average risk need to be screened to prevent one case of ovarian cancer by undergoing oophorectomy. The NNS for all treatment options, and for both breast and ovarian cancer outcomes, decreases as risk for mutations increases. For women with high risk, the NNS to prevent one case of breast cancer by using a SERM is 211 (91-1,043), mastectomy 182 (107-435), and oophorectomy 68 (34-4,204); and the NNS to prevent one case of ovarian cancer by undergoing oophorectomy is 189 (100-15,565). Under the assumptions of the outcomes table, if 100,000 women in the general population underwent screening for *BRCA* mutations, 16 cases of breast cancer would be prevented using mastectomy and 31 cases of ovarian cancer would be prevented using oophorectomy (Figure 11).

Adverse effects are also described in Table 13. The number needed to treat with SERMs to cause a thromboembolic event each year is 1,042 (641-2,719), and to cause a case of endometrial cancer each year is 2,686 (1,228-15,726) (tamoxifen only). Use of chemoprevention is a long-term prevention strategy, so these estimates require adjustment depending on the projected length of therapy. Only 5 women need to be treated with mastectomy in order to have one surgical complication, and 20 with oophorectomy. The numbers of women undergoing treatment and experiencing adverse effects increase with each successive risk group.

Sensitivity analyses indicate that preventing breast and ovarian cancer cases that occur by age 40 to 50 require higher NNS than those that occur by age 75, although women in the high-risk group have a much lower NNS than those in lesser risk groups (Appendix S). In general, the

NNS for Ashkenazi Jewish women is lower than in the general population (Appendix S). Also, the prevalence ratios of *BRCA1* and *BRCA2* do not substantially influence the NNS, and if lower prevalence assumptions are used, the NNS increases.

Chapter 4. Discussion

Conclusions

Little is known about *BRCA* mutations in the general population, and most data originate from studies of highly selected women with existing cancer or strong family histories of cancer. A primary care approach to screening has not yet been tested. Several tools determining individual risks for possessing mutations have been developed from databases of women with *BRCA* mutations. Mutation testing for those with 10% or more probability by these estimations is considered an appropriate threshold by experts in the field.[234] Risk assessment tools are recommended as an adjuvant to genetic counseling[100] and have not been widely evaluated for use in risk stratification in primary care settings. Women assessed as high risk in primary care settings may not necessarily be candidates for mutation testing, but could be offered more definitive risk assessment by referral to genetic counseling or application of detailed risk assessment instruments. Referral guidelines have been developed for use in primary care settings, however, no consensus or gold standard exists and their accuracy and effectiveness are not known. Risk assessment, genetic counseling, and mutation testing did not cause adverse psychological outcomes, and counseling improved distress and risk perception in the highly selected populations studied.

Although studies of *BRCA* mutation prevalence are limited, several studies of penetrance have been published for the general population as well as specific populations, such as Ashkenazi Jewish women. To determine estimates of cancer occurrence for women with average, moderate, and high family history risks for mutations to calculate benefits and adverse effects of screening, penetrance was estimated in a meta-analysis. This approach provided an alternative way to estimate penetrance from heterogeneous studies that used a variety of methods to estimate penetrance and utilized differing populations and techniques of *BRCA* mutation testing. The analysis considered *BRCA1* and *BRCA2* mutations separately and combined, Ashkenazi Jewish and general populations separately, ovarian and breast cancer outcomes, and penetrance to age 40 (breast cancer) or 50 (ovarian cancer) and age 75 (both breast and ovarian cancer).

Currently available prevention interventions for women identified with clinically significant *BRCA* mutations include intensive screening, chemoprevention with SERMs, and prophylactic mastectomy and oophorectomy. Randomized controlled trials of SERMs used different eligibility criteria utilizing family history information to varying degrees. None of the chemoprevention trials evaluated *BRCA* mutation status prospectively. A meta-analysis of chemoprevention trial results indicated a statistically significant effect of SERMs in preventing breast cancer and estrogen receptor-positive breast cancer. Results also indicated significantly increased risks for thromboembolic events and, for tamoxifen, endometrial cancer. Observational studies of prophylactic surgeries indicated reduced risk of breast and ovarian cancer in mutation carriers.

Since no trials of screening for *BRCA* mutations in the general population are available to provide direct measures of benefits and adverse effects, data obtained from the evidence synthesis were utilized in an outcomes table. Estimating prevalence and penetrance and

stratifying by average, moderate, and high family risk groups are attempts to determine the yield of screening in populations that would present to primary care clinicians. Applying these estimates to outcomes tables that consider treatment effects and adverse events provides calculations of benefits and adverse effects for main outcomes. The NNS to prevent one case of breast or ovarian cancer is high among low-risk women and decreases as risk increases, as expected. Adverse effects also increase as more women are subjected to therapies. Although the outcomes table estimations can be helpful in determining benefits and adverse effects, caution is necessary in extrapolating too far from the primary data. Data are limited in describing the range of risk associated with *BRCA* mutations, genetic heterogeneity, and moderating factors outside the gene, among many other limitations described below.

Limitations of the Literature and Analysis

The quality and generalizability of studies evaluated in the evidence synthesis vary substantially and may not support the assumptions made for the outcomes table. Although several risk assessment tools are available, most were designed for specialists and studies of their use and effectiveness in stratifying patients in primary care settings are lacking. Each method of risk stratification is subject to misclassification, and few data are available to guide clinicians in the best approach. Studies of the effectiveness of genetic counseling, as a second step in screening, on patient decisions and outcomes are also lacking.

Most studies of *BRCA* mutation testing were conducted on highly selected samples of women, many with preexisting breast or ovarian cancer or from previously identified kindreds when they were tested. The meta-analysis attempted to determine the effect of testing women selected for family history on penetrance estimates by separating studies that included women with a known cancer family history from unselected populations. Results were similar, although data were limited to make such comparisons (Table 6). Risk was often based on self-reported information, thus the accuracy of risk stratification is limited by the accuracy of reported family history in each study. In some cases, data to determine penetrance came exclusively from one study, and when multiple studies were available, they were heterogeneous. Estimates may therefore, be unreliable. Most studies used research laboratory techniques to detect clinically significant mutations that differ from the DNA sequencing available clinically, potentially underestimating prevalence by one-third.[27] Clinical significance of mutations was determined by each study, and was based on likely functional significance and/or previous evidence of increased cancer risk, although definitions were fairly consistent across studies (Appendix I). Most importantly, it is not known how the results of studies based on these highly selected women in research settings translate to a general screening population.

Data are also not available to determine the optimal age to test and how the age at testing influences estimates of benefits and adverse effects. All estimates in the outcomes table are based on cases of cancer, not mortality. It is not known whether screening for *BRCA* mutations reduces cause-specific or all cause mortality and improves quality of life. The harms associated with receiving a false negative test result (12-15% with DNA sequencing), or a result indicating mutations of unknown significance (approximately 13%), are not known.

The outcomes table does not include non-quantitative measures of benefit or harm including ELSI. Although a wide-range of ELSI topics has been identified, data are limited. Despite

concern about insurance and employment discrimination as a result of assessment or testing for *BRCA* mutations, little information is available to evaluate this risk. Existing data on benefits and adverse effects are drawn primarily from highly selected groups of well-educated Caucasian women who volunteer for studies. Very little data are available from women in the general population or minority women.

Existing evidence shows that most women do not experience adverse effects from *BRCA* risk assessment, counseling, and testing. In contrast, most seem to benefit from this process and report decreased breast cancer worry, decreased anxiety, and more accurate perceptions of breast cancer risk. However, the long-term impact is unknown because most studies followed patients for less than 1 year. In addition, current studies do not evaluate psychological aspects of medical outcomes, and little data are available on the impact of testing on family members.

Treatment effects are influenced by several variables that are not available and not easily factored into an outcomes table. The effectiveness of risk-reducing oophorectomy is dependent on the age at which the procedure is performed, and it becomes less effective when performed after menopause.[72] The type of treatment selected may vary with the mutation. Women with *BRCA1* mutations have a higher risk of ovarian cancer than those with *BRCA2* mutations[130] and may be more likely to elect oophorectomies. Chemoprevention is most effective in preventing estrogen receptor-positive breast tumors, although it has not been specifically evaluated in women with *BRCA* mutations. The proportion of estrogen receptor-positive tumors varies from 28% of those among women with *BRCA1* mutations to 63% with *BRCA2* mutations.[189] It is not known how these differences influence patient decisionmaking. Although estimates of patient compliance with different interventions in the outcomes table were based on findings in the research literature, these may be significantly different in practice.

There is limited information about the cost-effectiveness of screening programs. A systematic review of economic research of cancer genetics services identified 12 studies that included economic evaluation of some aspect of *BRCA1* or *BRCA2* mutation testing and/or follow-up interventions, and 3 studies related to familial breast cancer.[235] Studies focused on genetic testing and genetic counseling, and modeling health outcomes of intensive screening and prevention. Cost-effectiveness was mainly influenced by targeting genetic services for patients with a strong family history of cancer, and was affected by a number of other factors such as outcome measures used, estimated outcomes, mutation penetrance, mutation prevalence, accuracy and cost of testing, number of patients counseled per healthy mutation carrier, frequency of clinical surveillance, interventions used as well as their uptake and effectiveness, and the age at which the individual has testing and prophylactic surgery.

Future Research

In order to determine the appropriateness of risk assessment and screening for *BRCA* mutations in primary care, more information is needed about mutation prevalence and impact in the general population. Research has focused on highly selected women in referral centers and generally reported short-term outcomes. Issues such as access to testing, effectiveness of screening approaches including risk stratification, use of system supports, and patient acceptance and education require additional study. Who should perform risk assessment and genetic counseling services, how should it be done, and what skills are needed are unresolved questions.

Trials comparing types of providers and protocols could address these issues. What happens after patients are identified as high risk in clinical settings is also not known. The consequences of genetic testing on individuals and their relatives require more study. Well-designed investigations using standardized measures and enrolling subjects that reflect the general population, including minority women, are needed.

An expanded database or registry of patients receiving genetic counseling for inherited breast and ovarian cancer susceptibility or tested for *BRCA* mutations would provide useful information about predictors of cancer, response to interventions, and other modifying factors for cancer. Although all patients clinically tested in the U.S. through direct DNA sequencing utilize a single laboratory, a centralized database with key variables to address these issues is not maintained. Current research resources that may help address some of these questions include the National Cancer Institute-funded Cancer Genetics Network[87] and Breast and Ovarian Cancer Family Registries.[236]Additional data from women of varying socioeconomic, racial, and ethnic groups is needed. Currently available risk prediction tools and interventions may not apply to these populations.

Additional research on interventions is needed including chemoprevention trials of mutation carriers, evaluation of the effect of age at intervention on outcomes, and measurement of long-term outcomes. Studies of factors related to acceptance of preventive interventions based on genetic information would be useful, such as determining if cancer incidence in relatives is reduced because they adopt preventive interventions. This information could improve patient decisionmaking and lead to better health outcomes.

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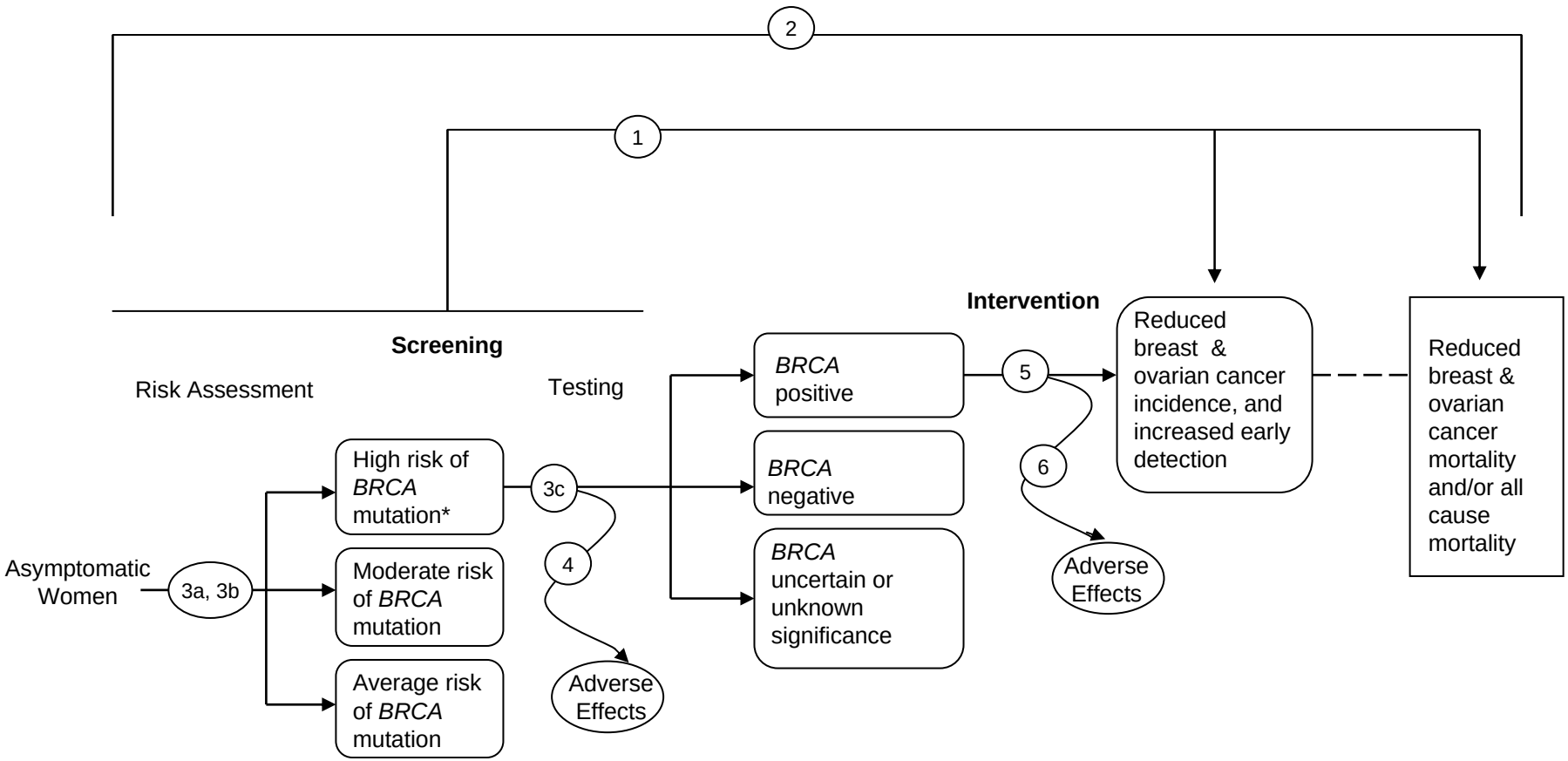
Figure 1. Analytic Framework



*Indicates clinically significant mutation of *BRCA1* or *BRCA2*

Figure 2. Key Questions

Key Question 1: Does risk assessment and *BRCA* mutation testing lead to a reduction in the incidence of breast and ovarian cancer and cause-specific and/or all cause mortality?

Key Question 2: What are the ethical, legal, and social implications of genetic screening for breast and ovarian cancer susceptibility?

Key Question 3a: How well does risk assessment for cancer susceptibility by a clinician in a primary care setting select candidates for *BRCA* mutation testing?

Key Question 3b: What are the benefits of genetic counseling prior to testing?

Key Question 3c: Among women with family histories predicting either an average, moderate, or high risk for a deleterious mutation, how well does *BRCA* mutation testing predict risk of breast and ovarian cancer?

Key Question 4: What are the adverse effects of risk assessment, counseling, and testing?

Key Question 5: How well do interventions reduce the incidence and mortality of breast and ovarian cancer in women identified as high-risk by history, positive genetic test results, or both?

Key Question 6: What are the adverse effects of interventions?

Figure 3. Relative Risk (RR) of Breast Cancer in Chemoprevention Trials

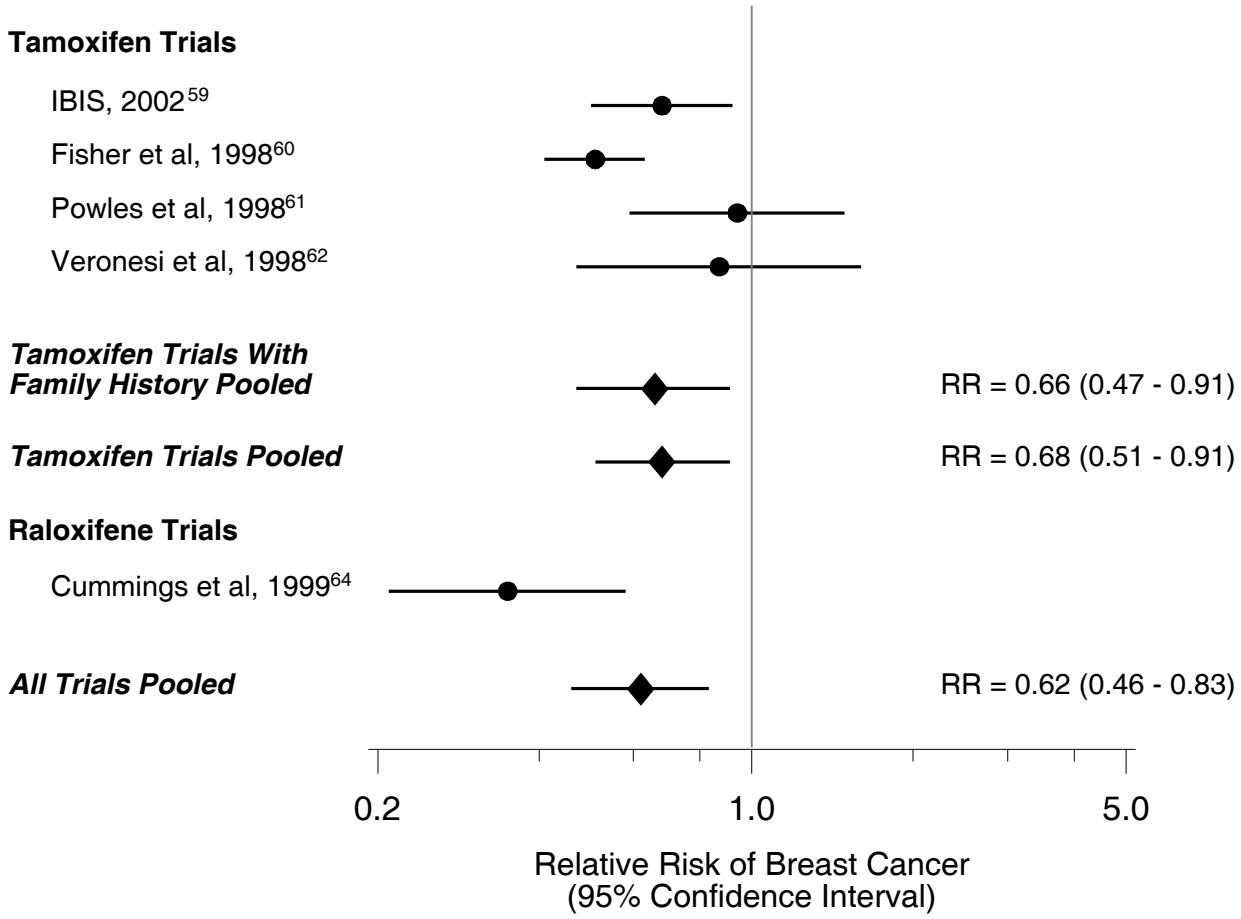


Figure 4. Relative Risk (RR) of Estrogen Receptor (ER) Positive Breast Cancer in Chemoprevention Trials

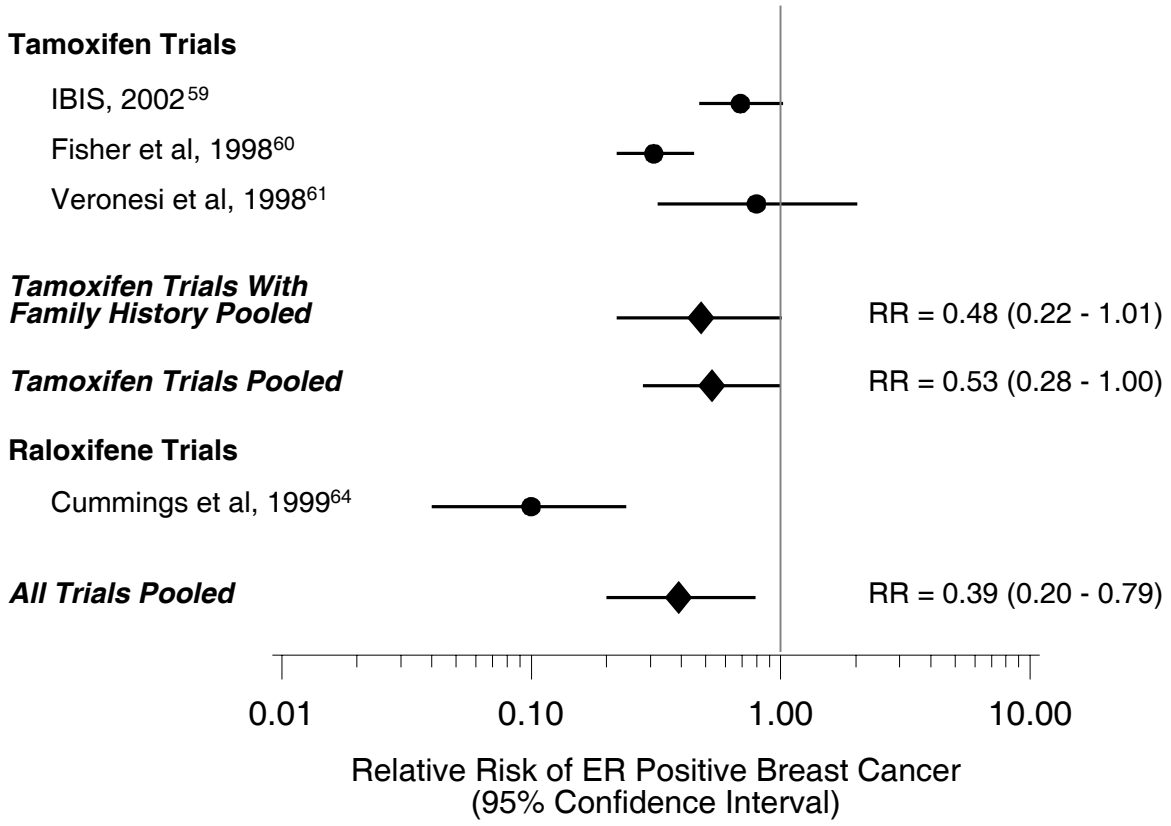


Figure 5. Relative Risk (RR) of Thromboembolic Events in Chemoprevention Trials

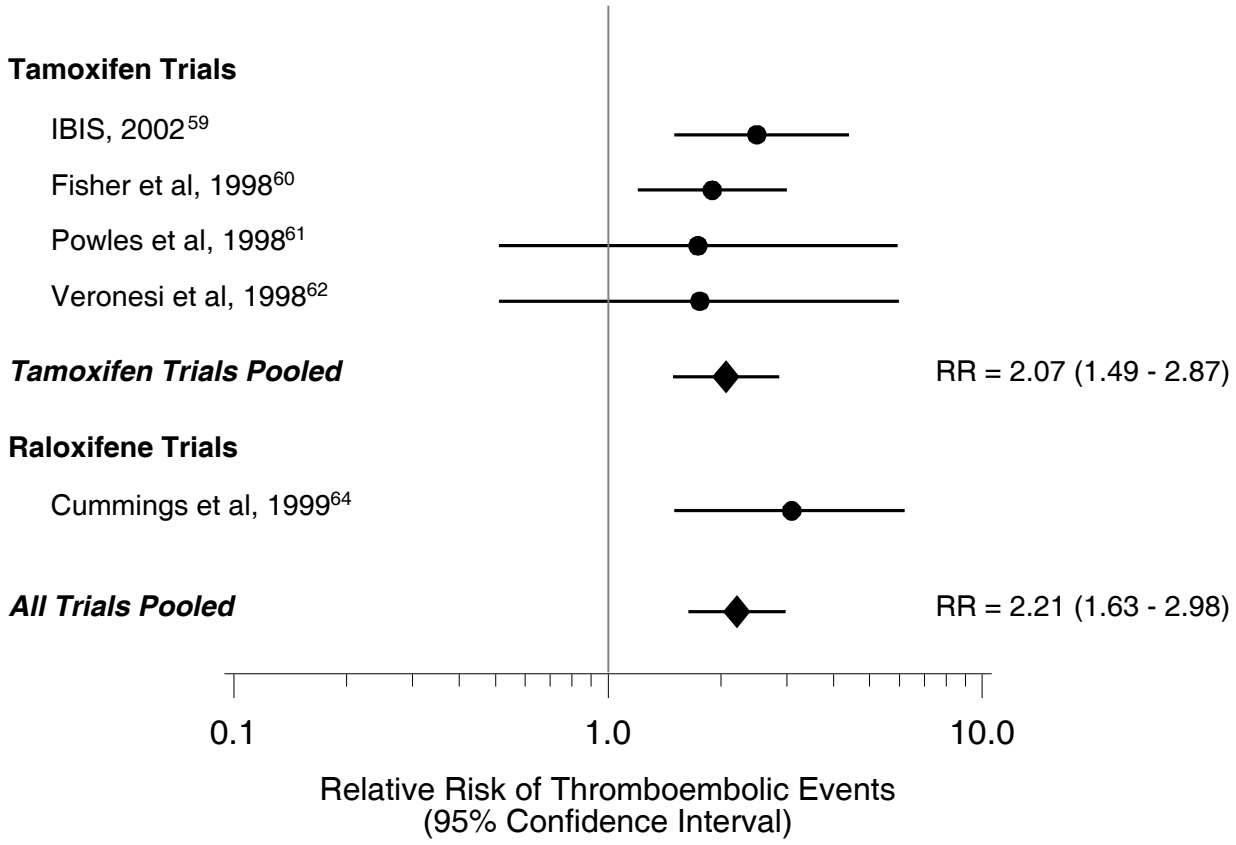


Figure 6. Relative Risk (RR) of Stroke in Chemoprevention Trials

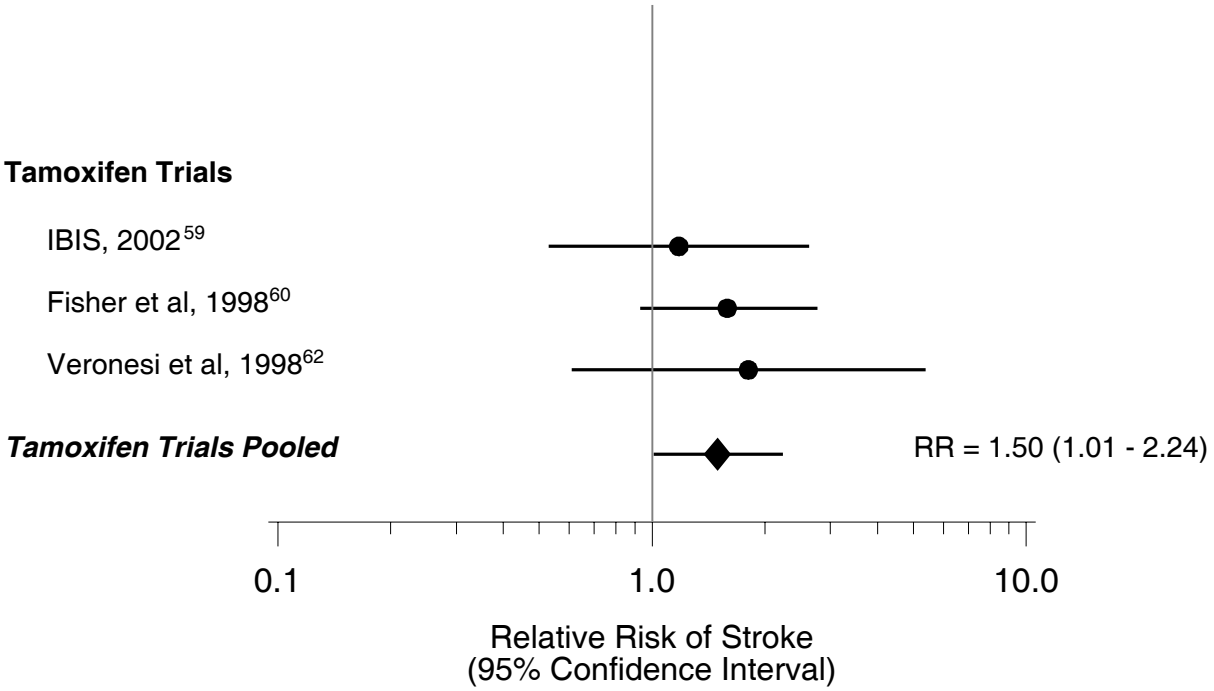
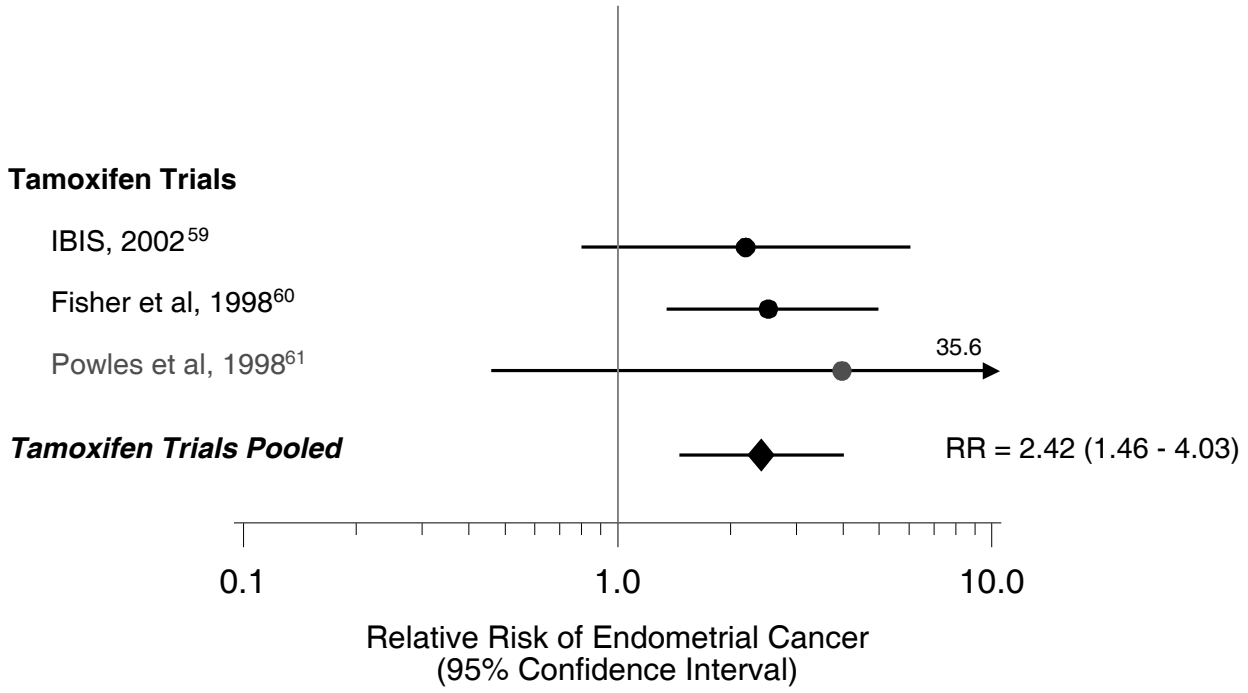


Figure 7. Relative Risk (RR) of Endometrial Cancer in Chemoprevention Trials



Figures 8. Relative Risk (RR) of All Cause Death in Chemoprevention Trials

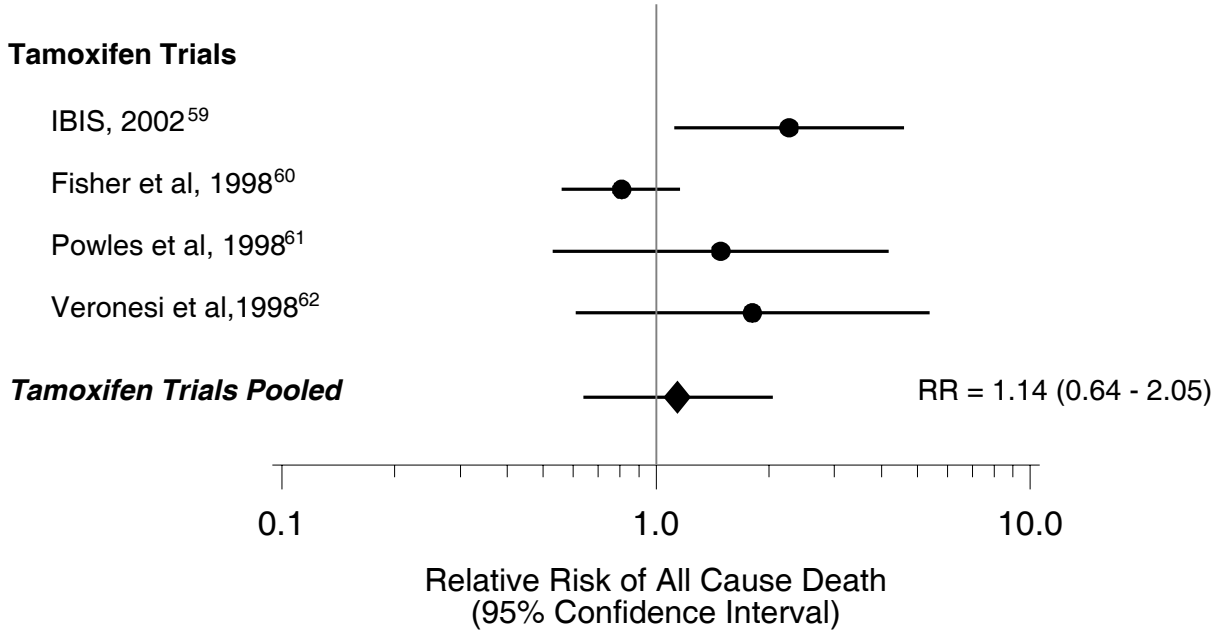
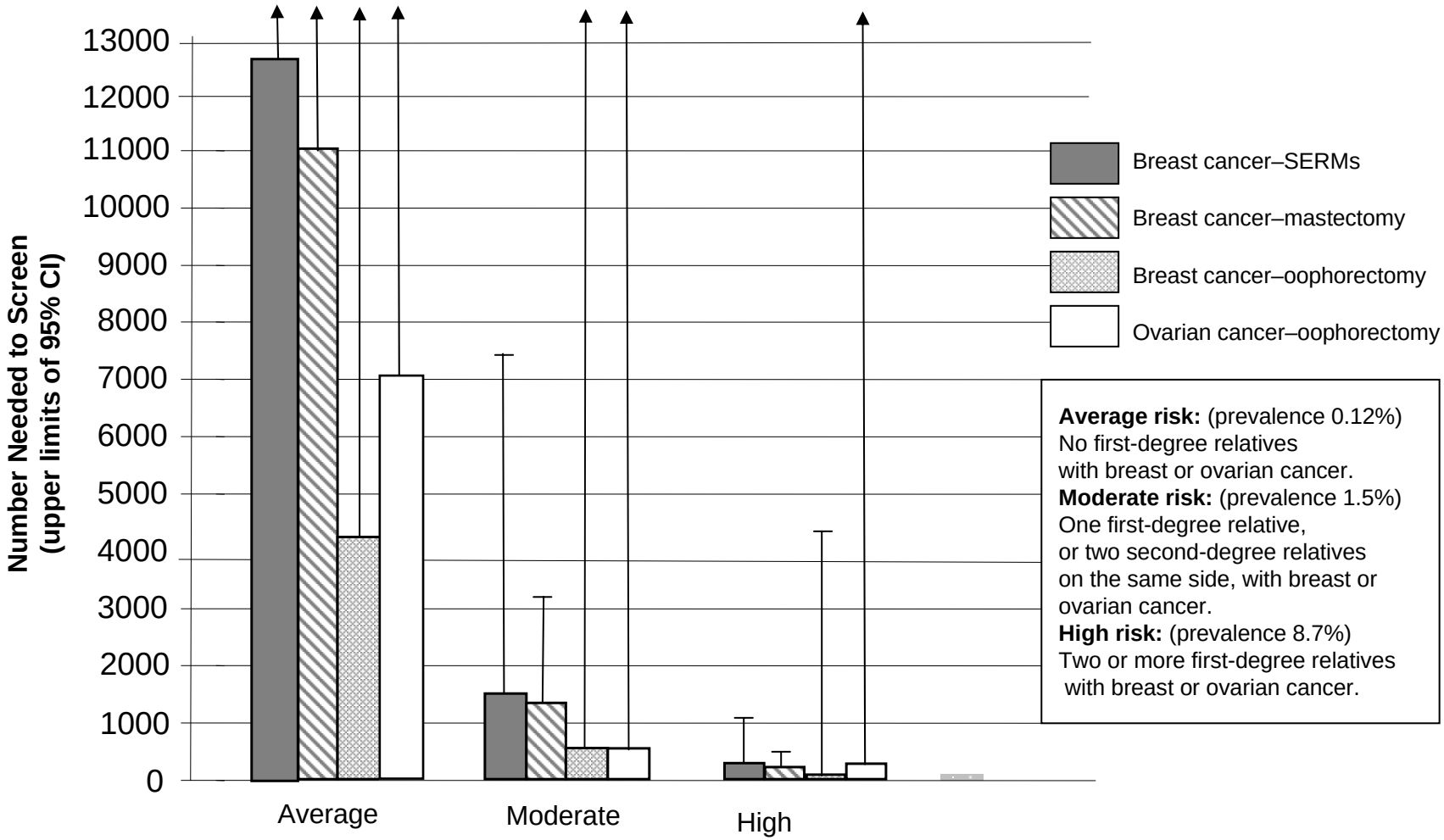
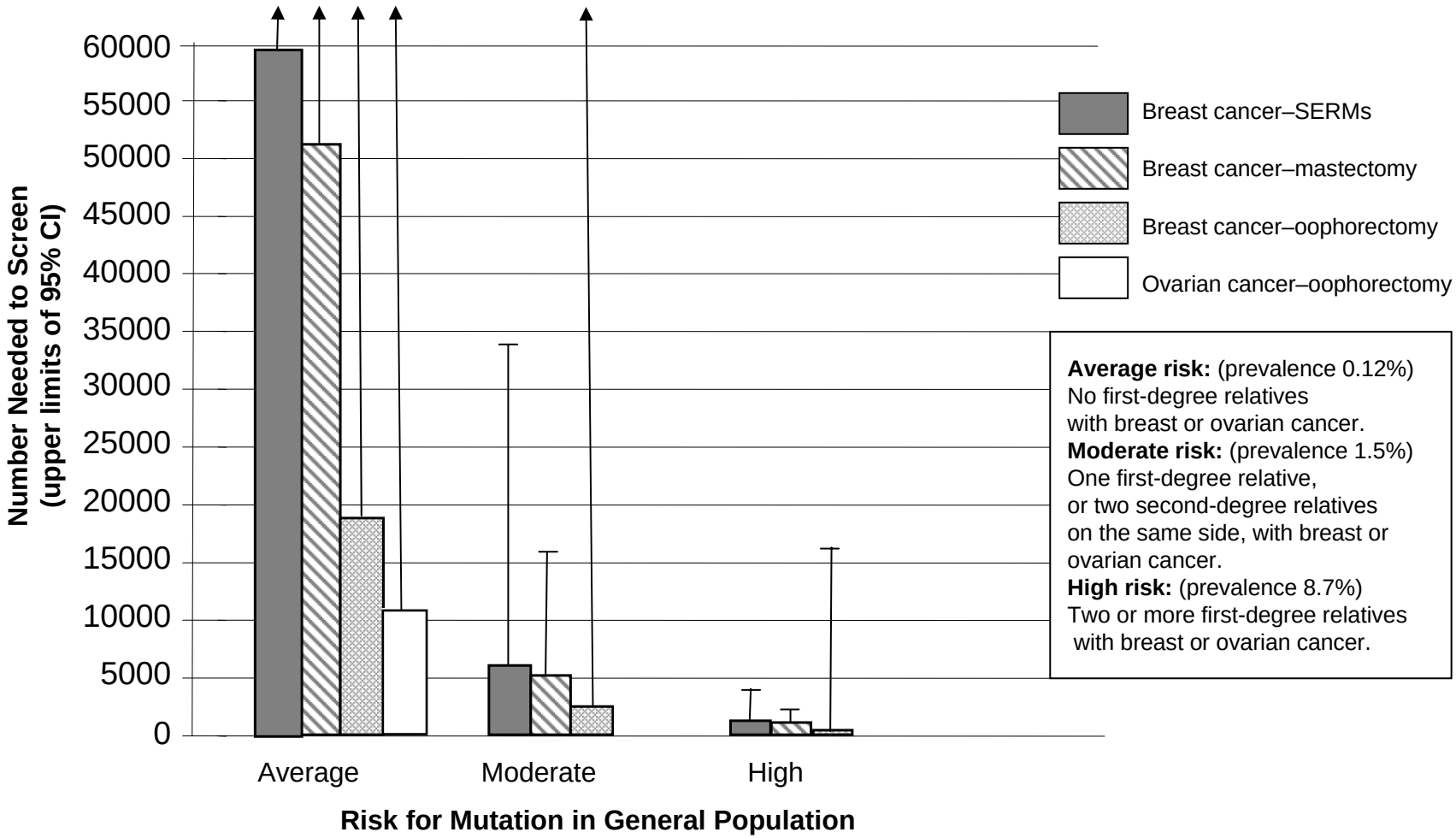


Figure 9. Number Needed to Screen for BRCA Mutations by Risk Groups to Prevent One Case of Breast or Ovarian Cancer to Age 75



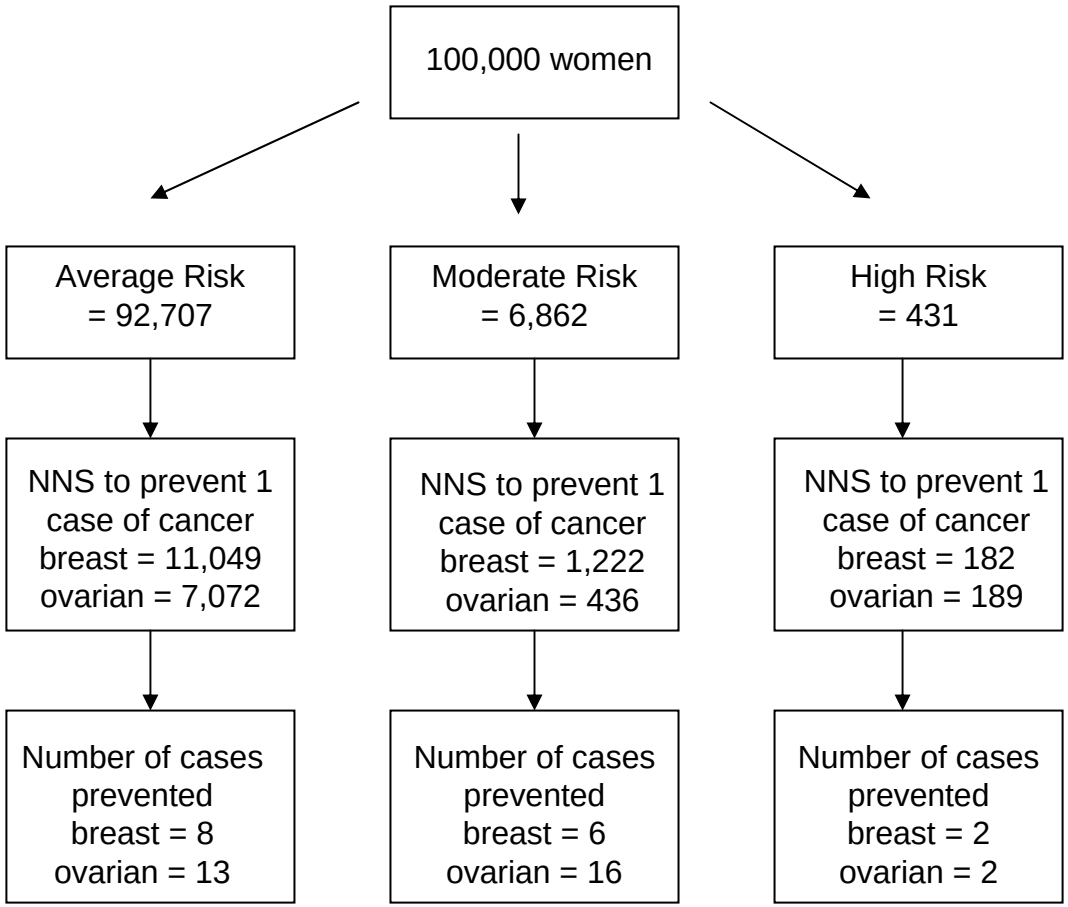
SERMs, selective estrogen receptor modulators.

Figure 10. Number Needed to Screen for BRCA Mutations by Risk Groups to Prevent One Case of Breast Cancer to Age 40 or Ovarian Cancer to Age 50



SERMs, selective estrogen receptor modulators.

Figure 11. Yield of Testing in A Hypothetical Population Based on Assumptions in Table 13



Total cases prevented = 16 breast cancer + 31 ovarian cancer

NNS, number needed to screen.

Table 1. Clinical Genetic Testing in the United States

Laboratory and Tool	Type of testing
Myriad Genetic Laboratories	DNA sequencing of entire coding region and targeted mutation analysis
Boston University School of Medicine Center for Human Genetics	Ashkenazi Jewish mutations only
Memorial Sloan-Kettering Cancer Center Diagnostic Molecular Genetics	Sequencing of select exons, targeted mutation analysis (mutations common in Ashkenazi Jewish population and sequencing of specific known mutations)
Mount Sinai School of Medicine Genetic Testing Laboratory (DNA Division)	Ashkenazi Jewish mutations only
New Jersey Medical School Center for Human and Molecular Genetics	Ashkenazi Jewish mutations only
University of California Los Angeles Diagnostic Molecular Pathology Laboratory	Targeted mutation analysis
University of California San Francisco Molecular Diagnostics Laboratory	Targeted mutation analysis
University of Chicago University of Chicago Genetic Services	Testing only for 185delAG and 5382insC or for known familial mutations
University of North Carolina Hospital Molecular Genetics	Protein truncation testing
University of Pittsburgh Medical Center Division of Molecular Diagnostics	Ashkenazi Jewish mutations only

Table 2. Tools to Assess Risk of *BRCA* Mutation

Tool	Reference	Administration	Applications	Description
Myriad Genetic Laboratories (*BRCA1*)	Shattuck-Eidens et al, 1997[35]	Questions	Proband must be affected with breast cancer and/or ovarian cancer. Applicable to families with small numbers of affected members.	Logistic regression model developed from data from early-onset breast and/or ovarian cancer and with a breast and/or ovarian cancer.
Myriad Genetic Laboratories (*BRCA1* and *BRCA2*)	Frank et al, 1998[94] Srivastava et al, 2001[34]	Questions	Proband must be affected with breast cancer < 50 years of age and/or ovarian cancer. Applicable to families with 2 first degree relatives with breast cancer < 50 years of age or ovarian cancer.	Logistic regression model developed from data from early onset breast cancer and/or ovarian cancer with second degree relatives with early breast or ovarian
Couch Model (*BRCA1* and *BRCA2*)	Couch et al, 1997[36] Blackwood et al, 2001[95]	Questions	Proband with or without breast or ovarian cancer. Applicable to families with ≥ 1 case(s) of breast cancer and Ashkenazi Jewish ancestry.	Logistic regression model based on data from wome with breast cancer and a family history of breast and cancer. Includes probability tables with estimates of finding a *BRCA1* mutation in individual families. Us diagnosis and considers Ashkenazi Jewish ancestry
BRCAPRO (*BRCA1* and *BRCA2*)	Berry et al, 1997,[96] 2002[97] Parmigiani et al, 1998[98] CancerGene[101]	Computer program	Proband may or may not have breast or ovarian cancer. Applicable to a variety of families.	Bayesian model utilizing first and second degree far including breast cancer, ovarian cancer, age at diag and size of family to estimate the age-specific proba *BRCA* mutation. Generates conditional or posterior Assuming that penetrance and prevalence functions BRCAPRO are accurate, it misses at most an estim mutations. Excludes paternal transmission of cance populations with families with breast cancer.

Table 2. Tools to Assess Risk of *BRCA* Mutation

Tool	Reference	Administration	Applications	Description
Cyrillic 3 Software Program (BRCAPRO and MENDEL)	www.cyrillicsoftware .com 102	Computer program	NR	Integrated risk assessment allows creation of pedigr individual, family, and disease data.
Progeny Software (*BRCA1* and *BRCA2)*	www.progeny2000. com237	Computer program	NR	Allows for creation of pedigrees for individual, family data.
Unnamed (*BRCA1* and *BRCA2*)	Tyrer et al, 2004[103]	Computer program	Proband may or may not have breast or ovarian cancer. Applicable to a variety of families.	Bayesian model incorporating *BRCA 1* and *BRCA2* penetrance gene, and personal risk factors to produ carrying genes predisposing to breast cancer, and tl likelihood of developing breast cancer.

NR, not reported.

Table 3. Criteria for Referral for Breast and Ovarian Cancer Genetic Counseling and Testing*

	HMO sites[†, 110]					Other groups‡									
Criteria supporting a referral for breast and ovarian cancer genetic counseling	**A**	**B**	**C**	**D**	**E**	**NCCN High Risk Assess-ment[112]**	**New York State ACMG[113]**	**UK Cancer Family Study Group[238]**	**Leiden WPHT[115]**	**Biomed 2 DPIBC[239]**	**Dept of Defense FBOCRP[240]**	**Oxford Regional Genetics Service[241]**	**All-Wales Cancer Genetics Service[242]**	**National Breast Cancer Centre[114]**	**Hampel Review[117]**
Women with a family history (but no personal history) of breast and/or ovarian cancer in maternal or paternal relatives as defined by at least one of the following:															
Breast cancer in at least 2 first- or second-degree relatives, with at least 2 diagnosed at age 49 or younger, and at least one of the relatives is first-degree.	X	X	X	X		X	X			X		X	X	X	X
Breast cancer in 3 or more first- or second-degree relatives, with at least one diagnosed at age 49 or younger.	X	X	X	X		X	X	X	X	X		X	X	X	X
Breast cancer in 1 or more first-degree relatives.					X	X	X								
Ovarian cancer in at least 2 first- or second-degree relatives, diagnosed at any age.	X	X	X	X		X	X						X	X	X

Table 3. Criteria for Referral for Breast and Ovarian Cancer Genetic Counseling and Testing*

	HMO sites[†, 110]					Other groups‡									
Criteria supporting a referral for breast and ovarian cancer genetic counseling	**A**	**B**	**C**	**D**	**E**	**NCCN High Risk Assess-ment[112]**	**New York State ACMG[113]**	**UK Cancer Family Study Group[238]**	**Leiden WPHT[115]**	**Biomed 2 DPIBC[239]**	**Dept of Defense FBOCRP[240]**	**Oxford Regional Genetics Service[241]**	**All-Wales Cancer Genetics Service[242]**	**National Breast Cancer Centre[114]**	**Hampel Review[117]**
Ovarian cancer in 1 or more first-degree relatives.					X	X	X								
Breast cancer in at least one first- or second-degree relative, and ovarian cancer in at least one first- or second-degree relative.	X	X	X	X		X	X	X		X		X	X	X	X
Delineates persons unacceptable for referral.	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Counseling required pre and/or post genetic test.	X	X	X		X	X	X	X		X	X			X	
Affected relative be tested first.			X		X										
Informed consent required prior to testing.	X	X	X	X	X										
Provides medical management recommendations for mutation carriers.	X		X	X	X	X	X	X		X	X	X			
Additional recommendations within the guideline.						X	X	X	X	X	X	X	X	X	X

Table 3. Criteria for Referral for Breast and Ovarian Cancer Genetic Counseling and Testing*

*Adapted from Mouchawar et al, 2003[110]

†Plans A, B, C, D: cancer genetic counseling referral guidelines for *BRCA* genes; E: counseling and testing guidelines for *BRCA* genes.

‡National Comprehensive Cancer Network (NCCN), 2003[112]; New York State Department of Health, American College of Medical Genetics (ACMG), 1999[113]; Leiden Working Party of Hereditary Tumors (WPHT), the Netherlands. Guidelines for women without breast cancer [115]; Biomed 2 Demonstration Programme on Inherited Breast Cancer (DPIBC), Norway[239]; Department of Defense Familial Breast/Ovarian Cancer Research Project (FBOCRP)240; National Health and Medical Research Council, National Breast Cancer Centre, 2000 Australia.[114]

Table 4. Randomized Controlled Trials of Genetic Counseling: Benefits, Adverse Effects, and Impact on Risk Perception

					Breast cancer worry	
Author, year	**N**	**History of cancer**	**Provider of genetic counseling**	**Measures**	**Increase**	**Decrease**
Bowen et al, 2004[38]	354	Family	Genetic Counselor or Mental Health Counselor	BCWS, BSI, SRE	0	X
Bowen et al, 2002[39]	357	Family	Genetic Counselor	SRE	NR	NR
Burke et al, 2000[40]	356	Family	Genetic Counselor	SRE	0	0
Cull et al, 1998*,[41]	144	NR	Genetic Counselor	GHQ, SRE, STAI	NR	NR
Green et al, 2004[120]	211	Family or Personal	Genetic Counselor or computer-based decision aid	NSI, SRE, STAI	NR	NR
Lerman et al, 1999[42]	364	Family	Nurse Educator	IES, NSI	0	X
Lerman, 1996[43]	124	Family	Nurse Educator	IES, POMS, SRE	0	X
Lerman et al, 1995[44]	227	Family	Nurse Educator	IES, SRE	0	X
Lobb et al, 2002*,[118]	195	Family, Personal, or None	Clinical Geneticist/Genetic Counselor	HADS, IES, SRE	0	0
Watson et al, 1998*,[119]	115	Family	Genetic Counselor	BCWS, GHQ, SRE	0	X¶

Table 4. Randomized Controlled Trials of Genetic Counseling: Benefits, Adverse Effects, and Impact on Risk Perception

	Anxiety		Depression		Perception of risk		Intention to participate in genetic testing		
Author, year	Increase	Decrease	Increase	Decrease	More accurate	Less accurate	Increase	Decrease	Quality rating
Bowen et al, 2004[38]	0	X	0	0	X	0	NR	NR	Fair
Bowen et al, 2002[39]	NR	NR	NR	NR	NR	NR	0	X	Fair
Burke et al, 2000[40]	NR	NR	NR	NR	X	0	NR	NR	Fair
Cull et al, 1998*, [41]	0	0	0	0	X†	X‡	NR	NR	Good
Green et al, 2004[120]	0	X	NR	NR	X	0	0	X§	Good
Lerman et al, 1999[42]	NR	NR	NR	NR	NR	NR	X‖	0	Fair
Lerman, 1996[43]	0	0	0	0	0	0	NR	NR	Fair
Lerman et al, 1995[44]	NR	NR	NR	NR	X	0	NR	NR	Fair
Lobb et al, 2002*, [118]	0	X¶	0	X¶	0	X#	NR	NR	Good
Watson et al, 1998*, [119]	0	0	0	0	X**	0	NR	NR	Good

BCWS, Breast Cancer Worry Scale; BSI, Brief Symptom Inventory; GHQ, General Health Questionnaire (12-, 28-, or 30-item); HADS, Hospital Anxiety and Depression Scale; IES, Impact of Events Scale (breast cancer specific distress); NSI, non-standardized instrument; POMS, Brief Profile of Mood States; SRE, Subject Risk Estimate (instrument not standardized, administration varies by study); STAI, State-Trait Anxiety Inventory.

X, significant relationship; 0, studied but not significant; NR, not reported.

* Study done in a country other than the United States (e.g. Scotland, Australia, or England).

† Both treatment groups at treatment end.

‡ Video after counseling subjects at 1-month follow-up.

§ Subjects in low-risk group only.

‖ African American subjects only.

¶ Subjects who listened to audio tape.

Unaffected subjects only.

** Risk provided as odds ratio.

Table 5. Results of Meta-Analysis of Prevalence Studies

Risk for mutation*	*BRCA1* No. studies	*BRCA1* Prevalence (%, 95% CI)	*BRCA2* No. studies	*BRCA2* Prevalence (%, 95% CI)	*BRCA1* or *BRCA2* No. studies	*BRCA1* or *BRCA2* Prevalence (%, 95% CI)
Average Risk		0.03†		0.03†		0.06†
		0.06†		0.06†		0.12†
		0.09†		0.09†		0.18†
	1[24]	0.12	1[24]	0.12	1[24]	0.24
Moderate Risk						
Ashkenazi Jewish	5[11, 12, 125-127]	0.82 (0.53, 1.28)	6[11, 12, 125-128]	1.13 (0.88, 1.44)	4[11, 12, 125, 127]	1.92 (1.31, 2.82)
General Population						
Low prevalence estimate	1[24]	0.12	1[24]	0.12	1[24]	0.24
		0.50†		0.50†		1.00†
		0.75†		0.75†		1.50†
		1.00†		1.00†		2.00†
		1.70†		1.70†		3.40†
High prevalence estimate	0	1.28‡	0	2.12‡	0	3.40‡
High Risk						
Ashkenazi Jewish	2[11, 129]	6.42 (1.13, 29.09)	2[11, 129]	1.10 (0.61, 1.98)	3[11, 33, 129]	10.25 (4.21, 22.86)
General Population	1[33]	4.34	1[33]	4.34	1[33]	8.68 (7.43, 10.11)

* Average risk = no first degree relatives with breast or ovarian cancer; moderate risk = one first degree relative with cancer or Ashkenazi Jewish without a first degree relative with cancer; high risk = two or more first degree relatives with cancer or Ashkenazi Jewish with one or more first degree relatives with breast or ovarian cancer.

† Sensitivity analysis.

‡ Results are obtained from Myriad Genetic Laboratories website and personal communications.

Table 6. Results of Meta-Analysis of Penetrance Studies of Breast Cancer

		BRCA1		*BRCA2*		*BRCA1* or *BRCA2*	
Risk for mutation*	**Age to develop cancer**	**No. studies**	**Penetrance (%, 95% CI)**	**No. studies**	**Penetrance (%, 95% CI)**	**No. studies**	**Penetrance (%, 95% CI)**
Average risk[†]	40[‖]	4[29, 141-143]	8.10[††] (5.29, 12.21)	2[29, 143]	7.48[††] (4.60, 11.96)	2[29, 143]	7.57[††] (5.43, 10.47)
Includes patients without family history PBRCA1= PBRCA2 = 0.12%	75	1[144]	52.18[††] (31.34, 72.29)	0	No data	1[#, 27]	31.57[††] (20.40, 45.37)
	40[‖]	4[29, 141-143]	10.51[††] (6.93, 15.65)	2[29, 143]	9.74[††] (6.04, 15.33)	2[29, 143]	9.85[††] (7.11, 13.49)
Includes patients without family history PBRCA1= PBRCA2 = 0.09%	75	1[144]	59.27[††] (37.84, 77.67)	0	No data	1[#, 27]	38.09[††] (25.46, 52.55)
	40[‖]	4[29, 141-143]	14.98[††] (10.04, 21.77)	2[29, 143]	13.93[††] (9.79, 21.36)	2[29, 143]	14.09[††] (10.30, 18.96)
Includes patients without family history PBRCA1= PBRCA2 = 0.06%	75	1[144]	68.58[††] (47.73, 83.91)	0	No data	1[#, 27]	47.99[††] (33.88, 62.42)
	40[‖]	4[29, 141-143]	26.06[††] (18.25, 35.75)	2[29, 143]	24.44[††] (16.16, 35.20)	2[29, 143]	24.67[††] (18.68, 31.87)
Includes patients without family history PBRCA1= PBRCA2 = 0.03%	75	1[144]	81.36[††] (64.61, 91.25)	0	No data	1[#, 27]	64.86[††] (50.62, 76.87)
	40[¶]	7[27, 29, 36, 132, 141-143]	9.60 [††] (4.80, 18.31)	4[27, 29, 132, 143]	7.38[††] (5.33, 10.15)	4[27, 29, 132, 143]	7.15[††] (5.67, 8.98)
Includes patients both selected for family history and without family history PBRCA1= PBRCA2 = 0.12%	75	2[142, 143]	54.10[††] (37.19, 70.12)	0	No data	1[#, 27]	31.57[††] (20.40, 45.37)
	40[¶]	7[27, 29, 36, 132, 141-143]	12.41 [††] (6.29, 23.01)	4[27, 29, 132, 143]	9.61[††] (6.98, 13.09)	4[27, 29, 132, 143]	9.31[††] (7.42, 11.63)
Includes patients both selected for family history and without family history PBRCA1= PBRCA2 = 0.09%	75	2[142, 143]	61.11[††] (44.11, 75.78)	0	No data	1[#, 27]	38.09[††] (25.46, 52.55)
	40[¶]	7[27, 29, 36, 132,	17.52 [††]	4[27, 29, 132, 143]	13.75[††]	4[27, 29, 132, 143]	13.35[††]

Table 6. Results of Meta-Analysis of Penetrance Studies of Breast Cancer

Risk for mutation*	Age to develop cancer	*BRCA1* No. studies	*BRCA1* Penetrance (%, 95% CI)	*BRCA2* No. studies	*BRCA2* Penetrance (%, 95% CI)	*BRCA1* or *BRCA2* No. studies	*BRCA1* or *BRCA2* Penetrance (%, 95% CI)
Includes patients both selected for family history and without family history PBRCA1= PBRCA2 = 0.06%		[141-143]	(9.15, 30.95)		(10.12, 18.42)		(10.73, 16.48)
	75	2[142, 143]	70.21†† (54.21, 82.44)	0	No data	1[#, 27]	47.99†† (33.88, 62.42)
	40¶	7[27, 29, 36, 132, 141-143]	29.82 †† (16.77, 47.27)	4[27, 29, 132, 143]	24.18†† (18.67, 31.11)	4[27, 29, 132, 143]	23.55†† (19.39, 28.30)
Includes studies of patients selected for family history and unselected patients PBRCA1= PBRCA2 = 0.03%	75	2[144, 145]	82.50†† (70.31, 90.37)	0	No data	1[#, 27]	64.86†† (50.62, 76.87)
Moderate risk							
General Population† PBRCA1= PBRCA2 = 0.12%	40**, ‡‡	5[29, 94, 141, 142]	48.71†† (25.89, 72.07)	3[94, 142]	36.50†† (26.50, 47.81)	4[29, 94, 142]	41.21†† (21.27, 64.53)
	75§§	1[143]	86.15†† (70.35, 94.22)	0	No data	1[#, 4]	76.83†† (61.56, 87.28)
General Population† PBRCA1= PBRCA2 = 0.5%	40 **, ‡‡	5[29, 94, 141, 142]	18.56†† (7.74, 38.25)	3[94, 142]	12.12†† (7.96, 18.03)	4[29, 94, 142]	14.40†† (6.09, 30.39)
	75§§	1[143]	59.88†† (36.29, 79.64)	0	No data	1[#, 4]	44.31†† (27.77, 62.22)
General Population† PBRCA1= PBRCA2 = 0.75%	40 **, ‡‡	5[29, 94, 141, 142]	13.19†† (5.29, 29.23)	3[94, 142]	8.42†† (5.45, 12.79)	4[29, 94, 142]	10.09†† (4.14, 22.54)
	75§§	1[143]	49.88†† (27.52, 72.29)	0	No data	1[#, 4]	34.66†† (20.40, 52.33)
General Population† PBRCA1= PBRCA2 = 1%	40 **, ‡‡	5[29, 94, 141, 142]	10.23†† (4.02, 23.65)	3[94, 142]	6.45†† (4.15, 9.91)	4[29, 94, 142]	7.76†† (3.14, 17.92)
Moderate risk							
PBRCA1= PBRCA2 = 1%	75§§	1[143]	42.74†† (22.17, 66.17)	0	No data	1[#, 4]	28.46†† (16.12, 45.16)

Table 6. Results of Meta-Analysis of Penetrance Studies of Breast Cancer

Risk for mutation*	Age to develop cancer	*BRCA1* No. studies	*BRCA1* Penetrance (%, 95% CI)	*BRCA2* No. studies	*BRCA2* Penetrance (%, 95% CI)	*BRCA1* or *BRCA2* No. studies	*BRCA1* or *BRCA2* Penetrance (%, 95% CI)
General Population[‡] PBRCA1= PBRCA2 = 1.7%	40**,[‡‡]	5[29, 94, 141, 142]	6.28[††] (2.41, 15.41)	3[94, 142]	3.90[††] (2.48, 6.07)	4[29, 94, 142]	4.72[††] (1.87, 11.38)
	75[§§]		30.51 [††] (14.35, 53.50)				18.96[††] (1.02, 32.63)
General Population[‡] PBRCA1= 1.3% PBRCA2 = 2.1%	40**,[‡‡]	5[29, 94, 141, 142]	8.06[††] (3.12, 19.24)	3[94, 142]	3.17[††] (2.02, 4.98)	4[29, 94, 142]	4.72[††] (1.87, 11.38)
	75[§§]	1[143]	36.47 [††] (17.97, 60.08)	0	No data	1[#, 27]	18.96[††] (1.02, 32.63)
Ashkenazi Jewish Includes patients without family history	40	2[150, 151]	5.03 (1.85, 12.97)	1[151]	1.23 (0.40, 3.75)	3[86, 151, 153]	2.9 (1.55, 5.36)
	75	3[134, 138, 152]	38.83 (27.26, 51.80)	3[134, 138, 152]	24.89 (13.11, 42.14)	5[86, 125, 134, 138, 152]	30.39 (22.20, 40.04)
Ashkenazi Jewish Includes patients both selected for family history and without family history	40	7[134, 150-153]	9.55 (5.46, 16.18)	5[134, 137, 150, 152]	2.72 (1.62, 4.51)	8[82, 133, 136, 149-151]	5.02 (3.01, 8.26)
	75	7[134, 137, 138, 144, 152]	41.42 (27.80, 56.49)	6[134, 137, 138, 152]	24.17 (17.20, 32.84)	6[141, 142]	33.7 (24.10, 44.85)
High risk							
General Population[§]	40[¶¶]	2[36, 140]	11.29[††] (7.75, 16.16)	0	No data	1[33]	7.7 (6.49, 9.11)
	75[##]	4[36, 129, 140, 143]	60.53[††] (52.34, 68.17)	1[129]	53.00 [††] (42.20, 63.52)	3[33, 129, 145]	59.07 (44.35, 72.32)
High risk							
Ashkenazi Jewish	40[‡‡]	3[129, 150, 151]	6.88 (1.92, 21.78)	2[129, 151]	9.1 (4.11, 18.94)	5[33, 86, 128, 146, 153]	4.91 (1.93, 11.95)
	75[‖‖]	3[129, 134, 152]	44.14 (11.47, 82.82)	3[129, 134, 152]	57.44 (40.38, 72.89)	6[33, 86, 125, 128, 151, 153]	34.73 (17.60, 57.00)

Table 6. Results of Meta-Analysis of Penetrance Studies of Breast Cancer

Risk for mutation*	Age to develop cancer	*BRCA1* No. studies	*BRCA1* Penetrance (%, 95% CI)	*BRCA2* No. studies	*BRCA2* Penetrance (%, 95% CI)	*BRCA1* or *BRCA2* No. studies	*BRCA1* or *BRCA2* Penetrance (%, 95% CI)

* Average risk = no first degree relatives with breast or ovarian cancer; moderate risk = one first degree relative with cancer or Ashkenazi Jewish without a first degree relative with cancer; high risk = two or more first degree relatives with cancer or Ashkenazi Jewish with one or more first degree relatives with breast or ovarian cancer.

† The prevalence of *BRCA1* and *BRCA2* is assumed to be 0.12% in the unaffected population thus either *BRCA1* or *BRCA2* is 0.24%.

‡ The prevalence of *BRCA1* and *BRCA2* is assumed to be 1.7% in the unaffected population and either *BRCA1* or *BRCA2* is 3.4%.

§ The prevalence of *BRCA1* and *BRCA2* is assumed to be 4.34% in the unaffected population.

‖ The analysis includes 1 study with data < 45 yrs, two studies < 35 yrs.

¶ The analysis includes 2 study with data < 45 yrs, two studies < 35 yrs.

The analysis includes data from one study with population of < 55 yrs thus the penetrance of mutation is the probability of developing cancer by 55 yrs.

**Only one study has data directly on <40 yrs group. The analysis also includes 2 studies with data < 45 ys, two studies < 35 yrs

†† Prevalence of mutation from the control group is assumed to be fixed. The 95% CI of penetrance is narrower than it should be.

‡‡ Assuming the risk ratio is 2.53 by Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC), 2001,[85] which is the risk ratio for family history with one first-degree relative for the group of patients diagnosed between 35-39.

§§ Assuming the risk ratio is 1.8 by CGHFBC, 2001, which is the overall risk ratio for family history with one first-degree relative.

‖‖ Assuming the risk ratio is 2.1 by Pharoah et al, 1997,[8] which is the risk ratio for family history with at least one first-degree relative.

¶¶ Assuming the risk ratio is 5.26, by CGHFBC, 2001, which is the risk ratio for family history with two first-degree relatives for the group of patients diagnosed <35.

Assuming the risk ratio is 2.93, by CGHFBC, 2001, which is the overall risk ratio for family history with two first-degree relatives.

Table 7. Results of Meta-Analysis of Penetrance Studies of Ovarian Cancer

Risk for mutation*	Age to develop cancer	*BRCA1* No. studies	*BRCA1* Penetrance (%, 95% CI)	*BRCA2* No. studies	*BRCA2* Penetrance (%, 95% CI)	*BRCA1* or *BRCA2* No. studies	*BRCA1* or *BRCA2* Penetrance (%, 95% CI)
Average risk	50	0	No Data	0	No Data	0	No Data
Includes patients without family history PBRCA1= PBRCA2 = 0.12%	<75†	2 [#, 133]	17.10 (11.27, 25.10)	1 [133]	20.64¶ (12.95, 31.27)	1 [133, 147]	19.25¶ (13.68, 26.40)
	50	0	No Data	0	No Data	0	No Data
Includes patients without family history PBRCA1= PBRCA2 = 0.09%	<75†	2 [#, 133]	21.58 (14.48, 30.89)	1 [133]	25.75¶ (16.55, 37.76)	1 [133, 147]	24.12¶ (17.44, 32.36)
	50	0	No Data	0	No Data	0	No Data
Includes patients without family history PBRCA1= PBRCA2 = 0.06%	<75†	2 [#, 133]	29.21 (20.25, 40.13)	1 [133]	34.22¶ (22.93, 47.64)	1 [133, 147]	32.29¶ (24.06, 41.78)
	50	0	No Data	0	No Data	0	No Data
Includes patients without family history PBRCA1= PBRCA2 = 0.03%	<75†	2 [#, 133]	45.21 (33.68, 57.29)	1 [133]	50.99¶ (37.30, 64.54)	1 [133, 147]	48.82¶ (38.79, 58.94)
Includes patients both selected for family history and without family history PBRCA1= PBRCA2 = 0.12%	50	1 [133]	19.82 (14.48, 26.53)	1 [133]	4.90 (2.12, 10.92)	1 [133]	13.00 (9.61, 17.35)
	<75†	3 [#, 133]	17.09¶ (11.54, 24.56)	1 [133]	20.64¶ (12.95, 31.27)	1 [133, 147, 148]	19.25¶ (13.68, 26.40)
Includes patients both selected for family history and without family history PBRCA1= PBRCA2 = 0.09%	50	1 [133]	24.79 (18.42, 32.50)	1 [133]	6.42 (2.81, 14.05)	1 [133]	16.61 (12.41, 21.87)
	<75†	3 [#, 133]	21.55¶ (14.81, 30.27)	1 [133]	25.75¶ (16.55, 37.76)	1 [133, 147, 148]	24.12¶ (17.44, 32.36)
Includes patients both selected for family history and without	50	1 [132]	33.09 (25.29, 41.94)	1 [133]	9.34 (4.15, 19.69)	1 [133]	23.00 (17.53, 29.57)

Table 7. Results of Meta-Analysis of Penetrance Studies of Ovarian Cancer

Risk for mutation*	Age to develop cancer	*BRCA1* No. studies	*BRCA1* Penetrance (%, 95% CI)	*BRCA2* No. studies	*BRCA2* Penetrance (%, 95% CI)	*BRCA1* or *BRCA2* No. studies	*BRCA1* or *BRCA2* Penetrance (%, 95% CI)
family history PBRCA1= PBRCA2 = 0.06%	<75[†]	3[#, 133]	29.18[¶] (20.68, 39.44)	1[133]	34.22[¶] (22.93, 47.64)	1[133, 147, 148]	32.29[¶] (24.06, 41.78)
	50	1[133]	49.72 (40.38, 59.09)	1[133]	17.08 (7.97, 32.90)	1[133]	37.4 (29.83, 45.65)
Includes patients both selected for family history and without family history PBRCA1= PBRCA2 = 0.03%	<75[†]	3[#, 133]	45.18[¶] (34.28, 56.57)	1[133]	50.99[¶] (37.30, 64.54)	1[133, 147, 148]	48.82[¶] (38.79, 58.94)
Moderate risk							
General Population[‖]	50	0	No Data	0	No Data	0	No Data
PBRCA1= PBRCA2 = 0.12%	<75[†]	4[#,94, 133, 143, 147]	88.44[¶] (85.43, 90.90)	2[94, 133]	69.83[¶] (56.66, 80.36)	2[94, 133]	83.60[¶] (67.61, 92.56)
General Population[‖]	50	0	No Data	0	No Data	0	No Data
PBRCA1= PBRCA2 = 0.5%	<75[‡]	4[#,94, 133, 143, 147]	64.75[¶] (58.46, 70.56)	2[94, 133]	35.71[¶] (23.88, 49.59)	2[94, 133]	55.03 (33.38, 74.92)
General Population[‖]	50	0	No Data	0	No Data	0	No Data
PBRCA1= PBRCA2 = 0.75%	<75[‡]	4[#,94, 133, 143, 147]	55.05[¶] (48.41, 61.51)	2[94, 133]	27.03[¶] (17.30, 39.60)	2[94, 133]	44.92 (25.04, 66.58)
General Population[‖]	50	0	No Data	0	No Data	0	No Data
Moderate risk							
PBRCA1= PBRCA2 = 1%	<75[‡]	4[#,94, 133, 143, 147]	47.87[¶] (41.30, 54.52)	2[94, 133]	21.74[¶] (13.56, 32.97)	2[94, 133]	37.96 (20.03, 59.90)

Table 7. Results of Meta-Analysis of Penetrance Studies of Ovarian Cancer

Risk for mutation*	Age to develop cancer	*BRCA1* No. studies	*BRCA1* Penetrance (%, 95% CI)	*BRCA2* No. studies	*BRCA2* Penetrance (%, 95% CI)	*BRCA1* or *BRCA2* No. studies	*BRCA1* or *BRCA2* Penetrance (%, 95% CI)
General Population‖	50	0	No Data	0	No Data	0	No Data
PBRCA1= PBRCA2 = 1.7%	<75‡	4[#,94, 133, 143, 147]	35.07¶ (29.27, 41.35)	2[94, 133]	14.04¶ (8.45, 22.44)	2[94, 133]	26.46 (12.84, 46.77)
General Population‖	50	0	No Data	0	No Data	0	No Data
PBRCA1= 1.3% PBRCA2 = 2.1%	<75‡	4[#,94, 133, 143, 147]	41.40¶ (35.12, 47.97)	2[94, 133]	11.68¶ (6.95, 18.97)	2[94, 133]	26.46 (12.84, 46.77)
Ashkenazi Jewish‖	50	0	No Data	0	No Data	0	No Data
Includes patients without family history	<75	0	No Data	0	No Data	1[135]	15.89 (10.46, 23.40)
Ashkenazi Jewish‖ Includes patients both selected for family history and without family history	50	3[135, 152, 154]	14.16 (9.17, 21.23)	3[135, 152, 154]	1.79 (0.88, 3.58)	3[135, 152, 154]	7.50 (4.91, 11.30)
	<75	5[127, 133, 135, 152, 154]	31.49 (21.91, 42.96)	5[127, 133, 135, 152, 154]	11.72 (8.16, 16.56)	5[127, 133, 135, 152, 154]	21.39 (14.9, 29.69)
High risk							
General Population‖	50	0	No Data	0	No Data	1[33]	4.03 (3.14, 5.16)
High risk							
General Population‖	<75§	2[141, 149]	26.14¶ (21.98, 30.76)	1[149]	6.43¶ (3.41, 11.82)	2[33, 149]	15.64 (12.88, 18.87)
Ashkenazi Jewish‖	50	0	No Data	0	No Data	1[33]	3.31 (1.34, 7.92)
	<75	1[135]	21.67 (4.84, 60.07)	1[135]	44.57 (28.06, 62.37)	2[33, 135]	18.11 (7.60, 37.30)

Table 7. Results of Meta-Analysis of Penetrance Studies of Ovarian Cancer

Risk for mutation*	Age to develop cancer	*BRCA1* No. studies	*BRCA1* Penetrance (%, 95% CI)	*BRCA2* No. studies	*BRCA2* Penetrance (%, 95% CI)	*BRCA1* or *BRCA2* No. studies	*BRCA1* or *BRCA2* Penetrance (%, 95% CI)
General Population**	50	0	No Data	0	No Data	1[33]	13.99 (11.16, 17.40)
	<75[§]	2[141, 149]	60.17[¶] (54.61, 65.48)	1[149]	22.70[¶] (13.09, 36.41)	2[33, 149]	44.19 (38.71, 49.82)

* Average risk = no first degree relatives with breast or ovarian cancer; moderate risk = one first degree relative with cancer or Ashkenazi Jewish without a first degree relative with cancer; high risk = two or more first degree relatives with cancer or Ashkenazi Jewish with one or more first degree relatives with breast or ovarian cancer.

[†] The prevalence of *BRCA1* and *BRCA2* is assumed to be 0.12% in the unaffected population thus either *BRCA1* or *BRCA2* is 0.24%.

[‡] The prevalence of *BRCA1* and *BRCA2* is assumed to be 1.7% in the unaffected population and either *BRCA1* or *BRCA2* is 3.4%.

[§] The prevalence of *BRCA1* and *BRCA2* is assumed to be 4.34% in the unaffected population.

[‖] In analysis of penetrance with family history (FH), the risk ratio of ovarian cancer with one relative is 3.1 by Stratton et al, 1998.[90] No RR (relative risk) is available for FH with two first degree relatives. Penetrance might be underestimated for the group with two first-degree relatives. Ovarian cancer prevalence in Ashkenazi Jews is assumed to be the same as white.

[¶] Prevalence of mutation from the control group is assumed to be fixed. The 95% CI of penetrance is narrower than it should be.

[#] The analysis includes 1 study with data < 70 yrs.

** In analysis of penetrance with FH, the risk ratio of ovariance cancer with more than one relative (either first or second) is 11.7 by Stratton et al, 1998.[90] No RR is available for FH with two first degree relatives.

Table 8. Distress Due to Adverse Effects of Risk Assessment and Testing

Author, year	Study design	N	History of cancer	Genetic counseling	Measures of distress	Breast cancer worry: First follow-up† Increase	Breast cancer worry: First follow-up† Decrease	Breast cancer worry: Final follow-up‡ Increase	Breast cancer worry: Final follow-up‡ Decrease
Risk Assessment									
Brain et al, 2002*, [156]	RCT	740	Family	Clinical Geneticist or Genetic Nurse Specialist	BCWS, STAI, NSI	0	X‖	NR	NR
Watson et al, 1999*, [163]	Pre-Post	303	Family	Unknown	BCWS, GHQ, IES, STAI, NSI	0	0	0	0¶
Hopwood et al, 1998*, [158]	Non-comparative	174	Family	Unknown	GHQ, NSI	NR	NR	NR	NR
Lobb et al, 2004*, [160]	Longitudinal	158	Family or Personal	Clinical Geneticist or Oncologist or Genetic Counselor	HADS, IES, NSI	X	0	NR	NR
Risk Assessment and Testing									
Friedman et al, 1999 [157]	Prospective Cohort	333	Family, Personal, or None	Genetic Counselor	IES, POMS-SF, NSI	0	X	0	X#
Meiser et al, 2002†, [161]	Prospective Cohort	143	Family	Unknown	BDI, IES, MBSS, STAI,	X**	0	X**	0
Testing									
Smith et al, 1999 [162]	Prospective Cohort	500	Family	Genetic Counselor	IES, NSI	NR	NR	NR	NR
Lerman et al, 1998 [159]	Prospective Cohort	396	Family or Personal	Physician	CES-D, IES	NR	NR	NR	NR
Bish et al, 2002*, [155]	Case Series	63	Personal	Specialist or Genetic Counselor	BCWS, GHQ, HADS, IES, NSI	0	0	0	0

Table 8. Distress Due to Adverse Effects of Risk Assessment and Testing

	Anxiety				Depression				
	First follow-up[†]		Final follow-up[‡]		First follow-up[†]		Final follow-up[‡]		
Author, year	**Increase**	**Decrease**	**Increase**	**Decrease**	**Increase**	**Decrease**	**Increase**	**Decrease**	**Quality rating**
Risk Assessment									
Brain et al, 2002*, [156]	0	0	NR	NR	NR	NR	NR	NR	Good
Watson et al, 1999*, [163]	0	X	0	0	0	0	0	0	Good
Hopwood et al, 1998*, [158]	0	0	0	0	0	0	0	0	Good/ Fair
Lobb et al, 2004*, [160]	0	X	NR	NR	0	X	NR	NR	Good
Risk Assessment and Testing									
Friedman et al, 1999[157]	0	X	0	X	NR	NR	NR	NR	Fair
Meiser et al, 2002[†, 161]	0	X[††]	0	X**	0	X[††]	0	0	Good
Testing									
Smith et al, 1999[162]	X	0	NR	NR	NR	NR	NR	NR	Fair
Lerman et al, 1998[159]	NR	NR	NR	NR	X[‡‡]	X[††]	X[‡‡]	X[††]	Fair
Bish et al, 2002*, [155]	0	0	0	0	0	0	0	0	Fair

Table 8. Distress Due to Adverse Effects of Risk Assessment and Testing

BCWS, Breast Cancer Worry Scale; BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; GHQ, General Health Questionnaire (12-, 28-, or 30-item); HADS, Hospital Anxiety and Depression Scale; IES, Impact of Events Scale; MBSS, Miller Behavioural Style Scale; NSI, non-standardized instrument; POMS-SF, Profile of Moods State – Short Form; STAI, State-Trait Anxiety Inventory.

X, statistically significant relationship; 0, studied but not significant; NR, not reported.

*Study done in a country other than the United States (e.g. England, Wales, or Australia).

†First follow-up was immediate to 2 weeks: Bish et al, 2002; Brain et al, 2002; Smith et al, 1999; 4 weeks: Lobb et al, 2004; 1 month: Watson et al, 1999; Friedman et al, 1999; Lerman et al, 1998; 3 months: Hopwood et al, 1998; 4 months: Meiser et al, 2002.

‡Final follow-up was 6 months for all studies except Hopwood, 1998 and Meiser, 2002, which were 12 months.

‖Low and moderate risk subjects only.

¶Breast cancer worry not changed at final follow-up but perception of breast cancer worry as a problem was significantly reduced.

#Average risk subjects only.

**Mutation carriers only.

††Non-carriers only.

‡‡Subjects with high baseline distress who declined test result.

Table 9. Intensive Screening Studies in Women With Familial Breast Cancer Risk*

Author, year	No. of women (total/*BRCA* mutation carriers)	Inclusion criteria	Mean age at entry in years (range)	Screening method	Screening interval	Mean follow-up	Detection rate† per 1000	Sensitivity (%)
Brekelmans et al, 2001[173]	1198/128	FH+: RR > 2	38 (21-70)	Mam + CBE + MRI‡	6-monthly CBE + annual Mam + MRI‡	36 months	8.6	74
Chart and Franssen, 1997[174]	1044/UN	FH+ or combination of other risk factors	39.5/42.7 (2 populations)	Mam + CBE	Annual (high risk: 6-monthly CBE)	21.9 months	7.3	91
Gui et al, 2001[175]	1078/UN	FH+: lifetime risk > 1 in 6	45 (26-66)	Mam + CBE	Annual	UN	4.4	N/A
Kollias et al, 1998[176]	1371/UN	FH+: lifetime risk > 1 in 9	41 (18-49)	Mam + CBE	Annual CBE + biennial Mam	22 months	9.1	66
Komenaka et al, 2004[182]	UN/13	*BRCA* mutation carrier	46 (32-59)	Mam	Annual	UN	3	N/A
Lai et al, 1998[177]	2629/UN	Relative of case	UN (>35)	Mam + CBE	Annual	UN	5.7	UN
Lalloo et al, 1998[178]	1259/UN	FH+: lifetime risk > 1 in 6	39.1 (28-49)	Mam	Annual	30 months	5.5	87
Moller et al, 1996[179]	1194/UN	FH+ (see ref)	42.9	Mam	Annual	1.8 years	5.8	UN
Saetersdal et al, 1996[180]	537/UN	Dominant inheritance	42.5 (20-76)	Mam + CBE	1st-round results	N/A	15	N/A

Table 9. Intensive Screening Studies in Women With Familial Breast Cancer Risk*

Author, year	No. of women (total/*BRCA* mutation carriers)	Inclusion criteria	Mean age at entry in years (range)	Screening method	Screening interval	Mean follow-up	Detection rate† per 1000	Sensitivity (%)
Scheuer et al, 2002[183]	UN/165	*BRCA* mutation carrier	47.7 (24.1-79.0)	Mam + CBE + MRI‡	3-6 monthly CBE + annual Mam	24.1 months (range 1.6-66.0)	0.7	N/A
Tilanus-Linthorst et al, 2000[181]	678/UN	> 15% lifetime risk	42.9/43.3 (20-75)	Mam + MRI‡ + CBE	Annual (high risk: 6-monthly CBE)	3.3 years	9.3	92
Warner et al, 2004[55]	236/236	*BRCA* mutation carrier	46.6 (26.4-64.8)	Mam + MRI + Ultrasound + CBE	Annual with 6-month CBE	100% round 1; 58% round 2, 36% round 3	22.6	95 (all modalities combined)

CBE, clinical breast examination; FH, family history; Mam, mammography; MRI, magnetic resonance imaging; RR, relative risk; UN, unknown.

*Adapted from Brekelmans et al, 2001[173].

†For invasive breast cancers only.

‡In selected cases (dense breast tissue or *BRCA* carrier).

Table 10. Results of Chemoprevention Trials

Study	Subjects	N	Median follow-up (mo)	Breast cancer cases	Treatment No.	Treatment Rate*	Placebo No.	Placebo Rate*	Relative risk (95% CI)
Tamoxifen (20 mg per day)									
International Breast Cancer Intervention Study (IBIS-I) (IBIS, 2002)[59]	Increased breast cancer risk based on family history and other factors. Mean age 50.8 years; 40% using estrogen.	3573 tamoxifen 3566 placebo	50	Total	69		101		0.68 (0.50-0.92)
				Non-invasive	5		16		0.31 (0.12-0.82)
				Invasive	64		85		0.75 (0.54-1.04)
				ER positive	44		63		0.69 (0.47-1.02)
				ER negative	19		19		1.00 (0.53-1.87)
				Deaths	2		2		1.00 (0.14 -7.08)†
National Surgical Adjuvant Breast and Bowel Project P-1 Study (Fisher et al, 1998)[60]	Increased breast cancer risk by Gail model, age ≥60 years, or risk factors. 39% <50 years old; <10% using estrogen.	6576 tamoxifen 6599 placebo	55	Total	124		244		0.51 (0.41-0.63)†
				Non-invasive	35	1.4	69	2.7	0.50 (0.33-0.77)
				Invasive	89	3.4	175	6.8	0.51 (0.39-0.66)
				ER positive	41		130		0.31 (0.22-0.45)
				ER negative					NA
				Deaths	3		6		0.50 (0.13-2.01)†

Table 10. Results of Chemoprevention Trials

Study	Subjects	N	Median follow-up (mo)		Breast cancer cases				
					Treatment		Placebo		
					No.	Rate*	No.	Rate*	Relative risk (95% CI)
Tamoxifen (20 mg per day)									
Royal Marsden Hospital Trial (Powles et al, 1998)[61]	Family history of breast cancer <50 years old or in ≥2 relatives. Median age 47 years; 26% using estrogen.	1238 tamoxifen 1233 placebo	70	Total	34	4.7	36	5.0	0.94 (0.59-1.49)†
				Non-invasive					NA
				Invasive					NA
				ER positive					NA
				ER negative					NA
				Deaths	4		1		3.98 (0.45-35.59)
Italian Tamoxifen Prevention Study (Veronesi et al, 1998)[62]	Women with hysterectomy. Median age 51 years; 14% using estrogen.	2700 tamoxifen 2708 placebo	46	Total	19	2.1	22	2.3	0.87 (0.47-1.60)†
				Non-invasive					NA
				Invasive					NA
				ER positive	8		10		0.80 (0.32-2.03)†
				ER negative					NA
				Deaths	0		0		NS

Table 10. Results of Chemoprevention Trials

Study	Subjects	N	Median follow-up (mo)		Breast cancer cases				
					Treatment		Placebo		
					No.	Rate*	No.	Rate*	Relative risk (95% CI)
Raloxifene (60 or 120 mg per day)									
Multiple Outcomes of Raloxifene Evaluation (Cummings et al, 1999)[64]	Postmenopausal women with osteoporosis. Median age 66.9 years; 10% on estrogen.	5129 raloxifene 2576 placebo	40	Total	22	1.5	32	4.3	0.35 (0.21-0.58)
				Non-invasive	7		5		0.70 (0.22-2.21)†
				Invasive	13	0.9	27	3.6	0.24 (0.13-0.44)
				ER positive	4		20		0.10 (0.04-0.24)
				ER negative	7		4		0.88 (0.26-3.0)
				Deaths	1		0		NS

ER, estrogen receptor; NA, not available; NS, not statistically significant.

*Per 1,000 woman-years.

†Calculated.

Table 11. Results of Chemoprevention Trials--Adverse Effects

Study	Subjects	N	Median follow-up (mo)	Adverse effects	Treatment No.	Treatment Rate*	Placebo No.	Placebo Rate*	Relative risk (95% CI)
Tamoxifen (20 mg per day)									
International Breast Cancer Intervention Study (IBIS-I) (IBIS, 2002)[59]	Increased breast cancer risk based on family history and other factors. Mean age 50.8 years; 40% using estrogen.	3573 tamoxifen 3566 placebo	50	Thromboembolic event	43		17		2.5 (1.5-4.4)
				Pulmonary embolism	13		10		1.30 (0.57-2.96)†
				Deep vein thrombosis	24		5		4.79 (1.83-12.54)†
				Stroke	13		11		1.18 (0.53-2.63)†
				Endometrial cancer	11		5		2.2 (0.8-6.06)
				All cause death	25		11		2.27 (1.12-4.60)†
National Surgical Adjuvant Breast and Bowel Project P-1 Study (Fisher et al, 1998)[60]	Increased breast cancer risk by Gail model; age ≥60 years or risk factors. 39% <50 years old; <10% using estrogen.	6576 tamoxifen 6599 placebo	55	Thromboembolic event	53	NA	28	NA	1.90 (1.20-3.00)†
				Pulmonary embolism	18	0.69	6	0.23	3.01 (1.15-9.27)
				Deep vein thrombosis	35	1.34	22	0.84	1.60 (0.91-2.86)
				Stroke	38	1.45	24	0.92	1.59 (0.93-2.77)†
				Endometrial cancer	36	2.3	15	0.91	2.53 (1.35-4.97)
				All cause death	57	2.17	71	2.71	0.81 (0.56-1.16)†
Royal Marsden Hospital Trial (Powles et al, 1998)[61]	Family history of breast cancer <50 years old or in ≥2 relatives. Median age 47 years; 26% using estrogen.	1238 tamoxifen 1233 placebo	70	Thromboembolic event	7		4		1.74 (0.51-5.94)†
				Pulmonary embolism	3		2		1.49 (0.25-8.93)†
				Deep vein thrombosis	4		2		1.99 (0.37-10.86)†
				Stroke					NA
				Endometrial cancer	4		1		3.98 (0.46-35.59)†
				All cause death	9		6		1.49 (0.53-4.18)†
Italian Tamoxifen Prevention Study (Veronesi et al, 1998)[62]	Women with hysterectomy. Median age 51 years; 14% using estrogen.	2700 tamoxifen 2708 placebo	46	Thromboembolic event	7		4		1.76 (0.51-5.99)†
				Pulmonary embolism	1		1		1.00 (0.06-16.03)†
				Deep vein thrombosis	6		3		2.01 (0.50-8.01)†
				Stroke	9		5		1.81 (0.61-5.38)†
				Endometrial cancer					NA
				All cause death	6		9		0.67 (0.24-1.88)†

Study	Subjects	N	Median follow-up (mo)	Adverse effects	Treatment No.	Treatment Rate*	Placebo No.	Placebo Rate*	Relative risk (95% CI)
Raloxifene (60 or 120 mg per day)									
Multiple Outcomes of Raloxifene Evaluation (Cummings et al, 1999)[64]	Postmenopausal women with osteoporosis. Median age 66.9 years; 10% on estrogen.	5129 raloxifene 2576 placebo	40	Thromboembolic event	49		8		3.1 (1.5-6.2)
				Pulmonary embolism	17		3		2.85 (0.83-9.7)†
				Deep vein thrombosis	38		5		3.82 (1.50-9.69)†
				Stroke					NA
				Endometrial cancer	6		4		0.8 (0.2-2.7)
				All cause death					NA

NA, not available.

*Per 1,000 woman-years.

†Calculated.

Table 12. Summary of Evidence Table

Key question	Level of evidence	Conclusions	USPSTF quality	Generalizability
1. Does risk assessment and *BRCA* mutation testing lead to a reduction in the incidence of breast and ovarian cancer and cause-specific and/or all cause mortality?		No studies		
2. What are the ethical, legal, and social implications of genetic screening for breast and ovarian cancer susceptibility?	Observational studies and RCTs	Studies summarized under related key questions (3b, 4, 6)		
3a. How well does risk assessment for cancer susceptibility by a clinician in a primary care setting select candidates for *BRCA* mutation testing?	Descriptions of assessment tools and referral guidelines, only a few validation studies in populations of women at high risk	Assessment tools that estimate risk of *BRCA* mutation are available to clinicians, but most have not been evaluated in primary care settings. Several referral guidelines have been developed for primary care use but there is no consensus or gold standard for use. Studies of effectiveness in primary care settings are lacking.	Could not rate this design by USPSTF criteria	Tools developed from populations of women with breast and ovarian cancer
3b. What are the benefits of genetic counseling prior to testing?	RCTs with risk perception and distress outcomes	Genetic counseling may increase accuracy of risk perception and decrease breast cancer worry, anxiety, and depression.	Fair-good	Women in studies had all levels of risk, but were from highly selected specialty populations, white, and had high socioeconomic status.

Table 12. Summary of Evidence Table

3c. Among women with family histories predicting either an average, moderate, or high risk for a deleterious mutation, how well does *BRCA* mutation testing predict risk of breast and ovarian cancer?	Family linkage and population studies of prevalence and penetrance	Estimates of risk based on prevalence and penetrance can be stratified by family history risk groups that are applicable to screening. However, studies are heterogeneous and estimates based on them may not be reliable.	Could not rate this design by USPSTF criteria	Estimates most often from highly selected populations of women with breast and ovarian cancer
4. What are the adverse effects of risk assessment, counseling, and testing?	Observational studies and RCTs with distress outcomes	More studies showed decreased rather than increased distress after risk assessment, genetic counseling, and testing.	Fair-good	Women in studies had all levels of risk, but were from highly selected specialty populations, white, and had high socioeconomic status.
5. How well do interventions reduce the incidence and mortality of breast and ovarian cancer in women identified as high-risk by history, positive genetic test results, or both?		Relative risk or hazard ratio (95% CI)		
		Breast cancer cases		
Tamoxifen (20 mg per day)	Meta-analysis of 4 RCTs	0.68 (0.51-0.91)	Fair-good	3 trials included women with increased risk of breast cancer
Raloxifene (60 or 120 mg per day)	1 RCT	0.35 (0.21-0.58)	Good	Postmenopausal women with osteoporosis
Prophylactic mastectomy	Prosp cohort	0 (0-0.36); p<0.003	Fair	Women with *BRCA* mutations
Prophylactic oophorectomy	Retro cohort	0.47 (0.29-0.77)	Fair	Women with *BRCA* mutations
	Prosp cohort	0.32 (0.08-1.20)	Fair	Women with *BRCA* mutations
		Ovarian cancer cases		

Table 12. Summary of Evidence Table

	Retro cohort	0.04 (0.01-0.16)	Fair	Women with *BRCA* mutations
	Prosp cohort	0.15 (0.02-1.31)	Fair	Women with *BRCA* mutations
6. What are the adverse effects of interventions?				
Thromboembolism: tamoxifen and raloxifene	Meta-analysis of 5 RCTs	2.21 (1.63-2.98)	Fair-good	
Stroke: tamoxifen	Meta-analysis of 3 RCTs	1.50 (1.00-2.24)		
Endometrial cancer: tamoxifen	Meta-analysis of 3 RCTs	2.42 (1.46-4.03)		
All cause death: tamoxifen	Meta-analysis of 4 RCTs	1.14 (0.64-2.05)		
Surgical complications	Observational	21% Mastectomy 5% Ooophorectomy	Fair	Women with high family risk or *BRCA* mutations
Psychological harms	Descriptive	Patient satisfaction with surgery is mixed; cancer distress improves, but self-esteem, body image, and other outcomes are adversely affected in some women.	Could not rate this design by USPSTF criteria	Few studies, small study samples

Prosp, prospective; RCT, randomized controlled trials; Retro, retrospective; USPSTF, U.S. Preventive Services Task Force.

Table 13. Outcomes Table Summary

Assumptions	Risk level		
	Average	**Moderate**	**High**
Number of women screened	100,000	100,000	100,000
Prevalence of clinically significant *BRCA*mutations (%)			
BRCA1	0.06	0.75	4.34
BRCA2	0.06	0.75	4.34
Penetrance of mutation to age 40/50 (%)			
Breast cancer (to age 40 years)			
BRCA1	14.98 (10.04-21.77)	13.19 (5.29-29.23)	11.29 (7.75-16.16)
BRCA2	13.93 (9.79-21.36)	8.42 (5.45-12.79)	No data
Ovarian cancer (to age 50 years)			
BRCA1	33.09 (25.29-41.94)	No data	No data
BRCA2	9.34 (4.15-16.69)	No data	No data
Penetrance of mutation to age 75 (%)			
Breast cancer			
BRCA1	68.58 (47.73-83.91)	49.88 (27.52-72.29)	60.53 (52.34-68.17)
BRCA2	No data	No data	53.00 (42.20-63.52)
Ovarian cancer			
BRCA1	29.21 (20.25-40.13)	55.05 (48.41-61.51)	26.14 (21.98-30.76)
BRCA2	34.22 (22.93-47.64)	27.03 (17.30-39.60)	6.43 (3.41-11.82)
Risk reduction of SERMs to prevent all types of breast cancer, trials with mutation status unknown (RR=0.62; 0.46-0.83)	0.38 (0.17-0.54)	0.38 (0.17-0.54)	0.38 (0.17-0.54)
Risk of thromboembolic events from SERMs (% per year)	0.096 (0.036-0.156)	0.096 (0.036-0.156)	0.096 (0.036-0.156)
Risk of endometrial cancer from SERMs (% per year)	0.036 (0.00177-0.0709)	0.036 (0.00177-0.0709)	0.036 (0.00177-0.0709)
Proportion of candidates choosing SERMs (%) (not known)	Uniform (5, 50)	Uniform (5, 50)	Uniform (5, 50)
Risk reduction of mastectomy to prevent breast cancer if *BRCA* mutation (RR=0; 0-0.36)	0.91(0.64-1.00)	0.91(0.64-1.00)	0.91(0.64-1.00)
Risk of complications from mastectomy and reconstruction (% overall) (based on one study; range not known)	21	21	21
Proportion of candidates choosing mastectomy (%) (not known)	Uniform (5, 20)	Uniform (5, 20)	Uniform (5, 20)
Risk reduction of oophorectomy to prevent breast cancer if *BRCA* mutation (RR=0.32; 0.08-1.20)	0.68 (0.01-0.92)	0.68 (0.01-0.92)	0.68 (0.01-0.92)

Assumptions (continued)	Risk level		
	Average	**Moderate**	**High**
Risk of complications from oophorectomy (% overall) (based on one study; range not known)	5	5	5

Table 13. Outcomes Table Summary

Proportion of candidates choosing oophorectomy (%) (not known)	Uniform (25, 75)	Uniform (25, 75)	Uniform (25, 75)
Risk reduction of oophorectomy to prevent ovarian cancer in *BRCA*mutation (RR-0.15; 0.02-2.31)	0.85 (0.01-0.99)	0.85 (0.01-0.99)	0.85 (0.01-0.99)
Risk of complications from oophorectomy (% overall) (based on one study; range not known)	5	5	5
Proportion of candidates choosing oophorectomy (%) (not known)	Uniform (25, 75)	Uniform (25, 75)	Uniform (25, 75)
Outcomes–benefits to age 40 and 50			
Number of breast cancer cases expected among candidates if not undergoing treatment	17.5 (13.0-23.3)	164 (98-287)	1315 (845-2047)
Number of breast cancer cases prevented among candidates taking SERMs (using overall risk reduction of 0.38)	1.7 (0.33-4.1)	15.5 (2.9-44.6)	125 (24-335)
NNS to prevent 1 case of breast cancer using SERMs	59826 (24285-301547)	6438 (2243-34388)	801(300-4176)
NNT with SERMs to prevent 1 case of breast cancer	18.3 (11.3-43.2)	24.6 (12.3-63.2)	17.7 (9.8-43.6)
Number of breast cancer cases prevented among candidates undergoing mastectomy	1.9 (0.77-3.7)	18.0 (6.5-41.2)	145 (54-304)
NNS to prevent 1 case of breast cancer using mastectomy	51469 (27396-129503)	5548 (2426-15433)	691(329-1845)
NNT with mastectomy to prevent 1 case of breast cancer	7.5 (5.4-11.6)	10.1 (5.6-18.2)	7.3 (4.5-12.3)
Number of breast cancer cases prevented among candidates if undergoing oophorectomy	5.2 (0.0084-11.3)	49 (0.78-125)	393 (6-929)
NNS to prevent 1 case of breast cancer using oophorectomy	19067 (8820-1189273)	2045 (802-128155)	255 (108-16057)
NNT with oophorectomy to prevent 1 case of breast cancer	10.4 (6.5-692)	14.3 (7.0-928)	10.2 (5.5-670)
Number of ovarian cancer cases expected among candidates if not undergoing treatment	25.7 (19.7-33.5)	No data	No data
Number of ovarian cancer cases prevented among candidates undergoing oophorectomy	9.5 (0.12-18.8)	No data	No data
		Risk level	
Outcomes–benefits to age 40 and 50 (continued)	**Average**	**Moderate**	**High**
NNS to prevent 1 case of ovarian cancer using oophorectomy	10489 (5305-864679)	No data	No data
NNT with oophorectomy to prevent 1 case of ovarian cancer	5.7 (4.0-481)	No data	No data
Outcomes–benefits to age 75			
Number of breast cancer cases expected among candidates if not undergoing treatment	82 (65-96)	748 (508-989)	4925 (4341-5493)
Number of breast cancer cases prevented among candidates taking SERMs (using overall risk reduction of 0.38)	7.8 (1.6-18.4)	71 (14-177)	474 (96-1100)

Table 13. Outcomes Table Summary

NNS to prevent 1 case of breast cancer using SERMs	12862 (5425-64048)	1419 (567-7237)	211 (91-1043)
NNT with SERMs to prevent 1 case of breast cancer	3.9 (2.6-9.1)	5.4 (3.3-13.1)	4.7 (3.2-10.7)
Number of breast cancer cases prevented among candidates undergoing mastectomy	9.1 (3.7-16.0)	82 (32-157)	550 (230-943)
NNS to prevent 1 case of breast cancer using mastectomy	11049 (6243-27037)	1222 (639-3142)	182 (107-435)
NNT with mastectomy to prevent 1 case of breast cancer	1.6 (1.3-2.4)	2.2 (1.6-3.6)	1.9 (1.6-2.8)
Number of breast cancer cases prevented among candidates if undergoing oophorectomy	24.4 (0.39-50.4)	222 (3.5-486)	1483 (24-2990)
NNS to prevent 1 case of breast cancer using oophorectomy	4100 (1985-255926)	452 (206-28242)	68 (34-4204)
NNT with oophorectomy to prevent 1 case of breast cancer	2.2 (1.5-148)	3.1 (1.9-203)	2.6 (1.9-177.0)
Number of ovarian cancer cases expected among candidates if not undergoing treatment	38 (29-48)	616 (527-721)	1422 (1186-1718)
Number of ovarian cancer cases prevented among candidates undergoing oophorectomy	14.1 (0.17-27.7)	230 (2.8-431)	530 (6.4-1006)
NNS to prevent 1 case of ovarian cancer using oophorectomy	7072 (3610-584750)	436 (232-35652)	189 (100-15565)
NNT with oophorectomy to prevent 1 case of ovarian cancer	3.9 (2.7-323)	2.9 (2.3-248)	7.4 (5.5-624.3)
		Risk level	
Outcomes–adverse effects	**Average**	**Moderate**	**High**
Number of women taking SERMs	33 (7.3-59)	412 (92-733)	2386 (532-4242)
Number of cases of thrombotic events due to SERMs	0.032 (0.005-0.073)	0.40 (0.068-0.91)	2.29 (0.40-5.28)
NNT with SERMs to cause one thrombotic event	1042 (641-2719)	1042 (641-2719)	1042 (641-2719)
Number of cases of endometrial cancer due to SERMs	0.012 (0.00039-0.032)	0.15 (0.005-0.40)	0.87 (0.029-2.32)
NNT with SERMs to cause one case of endometrial cancer	2686 (1228-15726)	2686 (1228-15726)	2686 (1228-15726)
Number of women undergoing mastectomy	15.0 (6.4-23.6)	188 (80.6-294)	1085 (467-1703)
Number of women with complications from mastectomy	3.2 (1.4-4.9)	39.4 (16.9-61.8)	228 (98-358)
NNT with mastectomy to cause one complication	5	5	5
Number of women undergoing oophorectomy	60 (32-89)	750 (394-1106)	4342 (2279-6401)
Number of women with complications from oophorectomy	3.0 (1.6-4.4)	37.5 (19.7-55.3)	217 (114-320)
NNT oophorectomy to cause one complication	20	20	20

NNS, number needed to screen; NNT, number needed to treat;
SERMs, selective estrogen receptor modulators.

Appendix A. Search Strategies

MEDLINE®--1966 to October 1, 2004

Ethical, Legal and Social Implications of Genetic Screening

1 exp Breast Neoplasms/ or exp ovarian neoplasms
2 exp Mass Screening/ or gene.mp. or genes.mp. or genetic$.mp. or BRCA$.mp.
3 exp LEGISLATION
4 exp JURISPRUDENCE
5 lj.fs.
6 3 or 4 or 5
7 exp bioethical issues/ or exp bioethics/ or ethic$.mp. or bioethic$.mp.
8 exp human rights
9 6 or 7 or 8
10 1 and 2 and 9
11 limit 10 to (human and English language)

Genetic Screening

1 exp Preventive Medicine
2 exp Family Practice
3 exp Primary Health Care
4 exp Physicians, Family
5 1 or 2 or 3 or 4
6 exp Breast Neoplasms/ or exp ovarian cancer
7 exp Genetic Predisposition to Disease
8 exp Genetic Screening
9 6 and (7 or 8)
10 exp Breast Neoplasms/ge or exp ovarian cancer/ge [Genetics]
11 9 or 10
12 5 and 11

Genetic Counseling

1 exp Genetic Counseling/ or Genetic counseling.mp. or genetic counselling.mp.
2 decision making.mp. or exp Decision Making
3 exp RISK
4 risk$.mp.
5 exp Breast Neoplasms/ or breast neoplasm$.mp. or Breast cancer$.mp. or exp ovarian neoplasms/ or ovarian cancer$.mp. or ovarian neoplasm$.mp.
6 1 and (2 or 3 or 4) and 5

Prediction of Disease Occurrence

1 exp Breast Neoplasms/mo, pc, ep, eh or exp ovarian neoplasms/mo, pc, ep, eh [Mortality, Prevention & Control, Epidemiology, Ethnology]
2 exp GENES, BRCA1/ or exp BRCA1 PROTEIN/ or BRCA1.mp.
3 exp GENES, BRCA2/ or exp BRCA2 PROTEIN/ or BRCA2.mp.
4 2 or 3
5 exp Breast Neoplasms/ge or exp ovarian neoplasms/ge [Genetics]

6 (sensitivity and specificity).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
7 exp "Sensitivity and Specificity"
8 risk$.mp. or exp RISK
9 5 and (6 or 7 or 8)
10 1 and 4 and 9

Prediction Models

1 (gail adj model$).mp. [mp=title, abstract, name of substance, mesh subject heading]
2 (claus adj model$).mp. [mp=title, abstract, name of substance, mesh subject heading]
3 1 or 2
4 exp Models, Statistical
5 exp risk
6 exp Breast Neoplasms/ge [Genetics]
7 4 and 5 and 6
8 3 or 7
9 limit 8 to human
10 limit 9 to English language
11 limit 9 to abstracts
12 10 or 11

BRCA Studies

1 exp case-control studies
2 brca$.mp.
3 1 and 2
4 exp Breast Neoplasms
5 exp Ovarian Neoplasms
6 4 or 5
7 3 and 6

Harms of Risk Assessment and Testing

1 exp Breast Neoplasms/ or exp ovarian neoplasms
2 exp genetic screening/ae or exp genetic services/ae or exp genetic counseling/ae or exp genetic screening/px or exp genetic services/px or genetic counseling/px
3 exp Breast Neoplasms/ge or exp ovarian neoplasms/ge [Genetics]
4 psychological stress.mp. or exp Stress, Psychological
5 (1 and 2) or (3 and 4)

Interventions: General

1 exp Breast Neoplasms/nu, pc, dh, rt, dt, rh, su, th, tr or exp ovarian neoplasms/nu, pc, dh, rt, dt, rh, su, th, tr
2 exp Treatment Outcome/ or treatment outcome$.mp.
3 exp "Outcome Assessment (Health Care)"/ or outcome assessment$.mp.
4 1 or 2 or 3
5 exp Breast Neoplasms/mo, ep, eh or exp ovarian neoplasms/mo, ep, eh
6 exp Breast Neoplasms/ or exp ovarian neoplasms

7 exp MORTALITY/ or mortal$.mp. or mortality.fs.
8 exp INCIDENCE/ or incidence$.mp. or epidemiology.fs. or ethnology.fs.
9 7 or 8
10 6 and 9
11 5 or 10
12 exp RISK
13 risk$.mp.
14 exp Genetic Predisposition to Disease/ or genetic predisposition to disease$.mp.
15 pedigree.mp. or exp PEDIGREE
16 12 or 13 or 14 or 15
17 exp Breast Neoplasms/ge or exp ovarian neoplasms/ge
18 exp GENES, BRCA1/ or exp BRCA1 PROTEIN/ or BRCA1.mp.
19 exp GENES, BRCA2/ or exp BRCA2 PROTEIN/ or BRCA2.mp.
20 17 or 18 or 19
21 4 and 11 and 16 and 20

Interventions: Surgery

1 exp Breast Neoplasms/pc [Prevention & Control]
2 exp Ovarian Neoplasms/pc [Prevention & Control]
3 (mastectom$ or oophoectom$ or ovariectom$).mp. [mp=title, abstract, name of substance, mesh subject heading]
4 1 or 2
5 3 and 4
6 (family adj5 histor$).mp. [mp=title, abstract, name of substance, mesh subject heading]
7 exp Genetic Predisposition to Disease
8 brca.mp.
9 (BRCA1 or BRCA2).mp. [mp=title, abstract, name of substance, mesh subject heading]
10 6 or 7 or 8 or 9
11 5 and 10
12 limit 11 to human
13 limit 12 to English language
14 limit 12 to abstracts
15 13 or 14

Interventions: SERMs and Oral Contraceptives

1 exp Breast Neoplasms/pc [Prevention & Control]
2 exp Ovarian Neoplasms/pc [Prevention & Control]
3 1 or 2
4 (family adj5 histor$).mp. [mp=title, abstract, name of substance, mesh subject heading]
5 exp Genetic Predisposition to Disease
6 brca.mp.
7 (BRCA1 or BRCA2).mp. [mp=title, abstract, name of substance, mesh subject heading]
8 4 or 5 or 6 or 7
9 exp Selective Estrogen Receptor Modulators
10 (serm or serms or tamoxifen or raloxifene).mp. [mp=title, abstract, name of substance, mesh subject heading]

11 9 or 10
12 3 and 8 and 11
13 exp Contraceptives, Oral
14 3 and 8 and 13
15 12 or 14
16 limit 15 to human
17 limit 16 to English language
18 limit 16 to abstracts
19 17 or 18

Harms of Interventions

1 exp Breast Neoplasms/dt, su or exp ovarian neoplasms/dt, su
2 exp Breast Neoplasms/pc or exp ovarian neoplasms/pc
3 chemoprevention.mp. or exp CHEMOPREVENTION
4 primary prevention.mp. or exp Primary Prevention
5 2 or 3 or 4
6 postoperative complications.mp. or exp Postoperative Complications
7 intraoperative complications.mp. or exp Intraoperative Complications
8 ae.xs. or ct.fs.
9 psychological stress.mp. or exp Stress, Psychological
10 6 or 7 or 8 or 9
11 1 and 5 and 10

Appendix B. Inclusion/Exclusion Criteria By Key Question

Key Question 2 (Ethical, Legal, Social Implications)

Include	Randomized controlled trial
	Comparative study (cohort, case-control or observational study) with 50 or more subjects
Exclude	Not applicable to U.S. primary care setting
	Information not relevant (dated, off-topic)
	Anecdotal only, no data
	Single case report, letter, commentary, opinion
	Overview, meta-analysis, or review with relevant information
	Practice standards or guidelines
	Legal, with case study or data
	Regulations or legislation
	Background
	Policy
	Cost
	Background

Key Question 3a (Risk Assessment)

Include	Risk models
	Risk evaluation instrument
	Practice standards or guidelines
	Randomized controlled trial
	Comparative study (cohort, case-control or observational study) with 50 or more subjects
	Overview, meta-analysis, or review with relevant information
	Cost
Exclude	Not applicable to U.S. primary care setting
	Study limitations (small N, non-comparative, single case report)
	No data (commentary, letter, opinion)
	Information not relevant (dated, off-topic)

Key Question 3b (Genetic Counseling)

Include	Randomized controlled trials
Exclude	Not applicable to U.S. primary care setting
	Study limitations (small N, non-comparative, single case report)
	No data (commentary, letter, opinion)
	Information not relevant (dated, off-topic)
	Comparative study (cohort, case-control or observational study) with 50 or less subjects
	Overview, meta-analysis, or review with relevant information
	Practice standards or guidelines
	Cost

Key Question 3c (Genetic Testing)

Include	Genetic testing for heritable clinically significant *BRCA1* and/or *BRCA2* mutations (excludes tumor tissue only studies) Subjects from U.S., Canada, U.K., Australia, or Israel 50 or more subjects
Exclude	Risk model only No primary data included (include meta-analysis) Not *BRCA1* or *BRCA2* Not breast or ovarian cancer No genetic testing Only 2nd cancer at same site (risk of 2nd contralateral cancer) Basic science only (studies of gene function or gene expression) Tumor tissue only study Linkage and/or segregation analysis (i.e., no testing for *BRCA1* or *BRCA2* mutations)

Key Questions 5 and 6 (Interventions and Adverse Effects)

Include	Randomized controlled trial Comparative study (cohort, case-control or observational study) with 50 or more subjects Overview, meta-analysis, or review with relevant information Surveillance Chemoprevention Prophylactic surgery Cost
Exclude	Not applicable to U.S. primary care setting Study limitations (small N, non-comparative, single case report) No data (commentary, letter, opinion) Information not relevant (dated, off-topic)

Appendix C. U.S. Preventive Services Task Force (USPSTF) Quality Rating Criteria

Diagnostic Accuracy Studies

Criteria

- Screening test relevant, available for primary care, adequately described
- Study uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate results in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Administration of reliable screening test

Definition of ratings based on above criteria

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100) broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has important limitations such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.

Randomized Controlled Trials (RCTs) and Cohort Studies

Criteria

- Initial assembly of comparable groups**:** RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs

Definition of ratings based on above criteria

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Case Control Studies

Criteria

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variable

Definition of ratings based on above criteria

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.

Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80 percent or attention to some but not all important confounding variables.

Poor: Major selection or diagnostic work-up biases, response rates less than 50 percent, or inattention to confounding variables.

Appendix D. Statistical Methods

The meta-analysis of penetrance was based on Bayes' theorem and stratified by cancer type (breast or ovarian), risk group (average, moderate, and high), and age whenever enough data were available. The penetrance of *BRCA* mutations is the probability of developing cancer given that a clinically significant *BRCA* mutation is present. Let D^+ denote "individual has cancer," D^- denote "individual does not has cancer," G denote "individual has a clinically significant *BRCA* mutation," penetrance is then denoted as $P(D^+|G)$. By Bayes' theorem, penetrance is given by:

$$P(D^+ \mid G) = \frac{P(G \mid D^+)P(D^+)}{P(G)} = \frac{P(G \mid D^+)P(D^+)}{P(G \mid D^+)P(D^+) + P(G \mid D^-)P(D^-)} \qquad (1)$$

where $P(D^-) = 1 - P(D^+)$. In our analysis, we assume $P(D^+)$ is fixed. For the average risk group, the estimate of $P(D^+)$ from Surveillance, Epidemiology, and End Results (SEER) data is used in the calculation of penetrance. When family history is present, the estimate of $P(D^+)$ is obtained by multiplying the SEER estimate by the relative risk of cancer with a positive family history. $P(G|D^+)$ and $P(G|D^-)$ are the prevalences of *BRCA* mutations from the cancer-affected and cancer-unaffected populations respectively, and estimated from different studies using the meta-analysis approach as described above.

The 95% confidence interval of $P(D^+|G)$ is calculated as follows. Modifying equation (1), we have:

$$P(D^+ \mid G) = \frac{1}{1 + \dfrac{P(G \mid D^-)P(D^-)}{P(G \mid D^+)P(D^+)}} \qquad (2)$$

then, $\text{logit}\left(P(D^+ \mid G)\right) = \log\left(\dfrac{P(G \mid D^+)P(D^+)}{P(G \mid D^-)P(D^-)}\right)$. Assuming that $P(G|D^+)$ and $P(G|D^-)$ are independent with each other, standard calculation using delta-method shows:

$$\text{var}\left(\text{logit}\left(P(D^+ \mid G)\right)\right) = \frac{\text{var}\left(P(G \mid D^+)\right)}{P(G \mid D^+)^2} + \frac{\text{var}\left(P(G \mid D^-)\right)}{P(G \mid D^-)^2} \qquad (3)$$

Usually, $\text{logit}\left(P(D^+ \mid G)\right)$ is assumed to be normally distributed and the 95% confidence interval of $\text{logit}\left(P(D^+ \mid G)\right)$ is given as $\left(\text{logit}\left(P(D^+ \mid G)\right) \pm 1.96 \times \sqrt{\text{var}\left(\text{logit}\left(P(D^+ \mid G)\right)\right)}\right)$.

The 95% confidence interval of $P(D^+|G)$ is obtained by converting the above interval back to the original scale.

For some risk groups, there are no data from genetic testing studies to estimate $P(G|D^-)$ and we used the best point estimates available in the literature. However, standard errors associated with the point estimates are usually not available. Under such

conditions, the second part of (3) on the right hand side would be zero, and the 95% confidence interval for the penetrance would be underestimated.

Equation (1) provides the formula to calculate penetrance for cases in general. It is easy to extend (1) to calculate penetrance of *BRCA* mutations by a particular age or with a positive family history. For example, if we are interested in penetrance of *BRCA* mutations by Age *x*, we substitute D^+ by D^+ by Age *x* in equation (1)

$$P(D^+ \text{ by age } x \mid G) = \frac{P(G \mid D^+ \text{ by age } x)P(D^+ \text{ by age } x)}{P(G \mid D^+ \text{ by age } x)P(D^+ \text{ by age } x) + P(G \mid (D^+ \text{ by age } x)^-)(1 - P(D^+ \text{ by age } x))}. \quad (4)$$

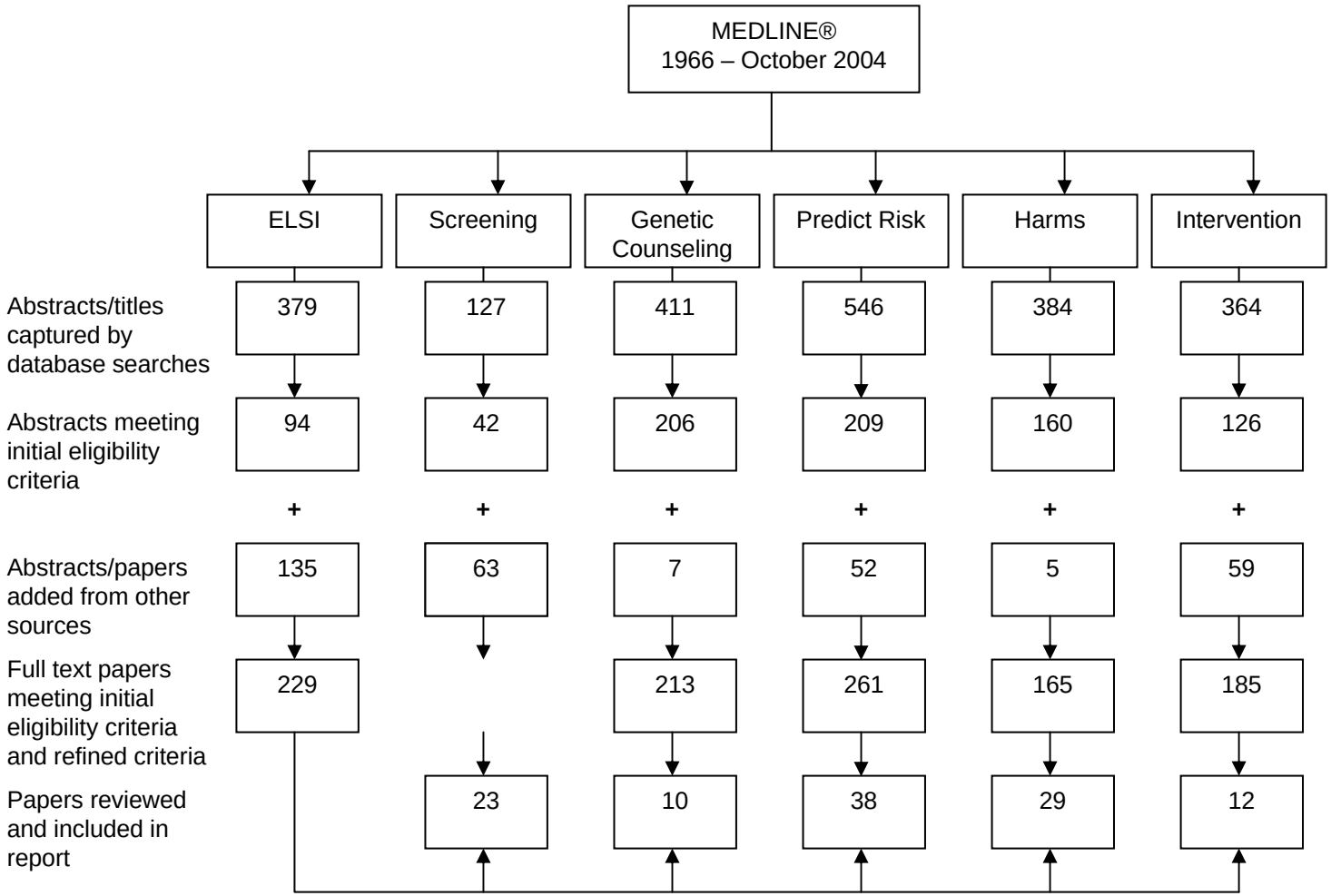
In this analysis, we assume $P(G \mid (D^+ \text{ by age } x)^-) \approx P(G \mid D^-)$.

In our analysis, we calculated penetrance of breast cancer to ages 40 and 75 and ovarian cancer to ages 50 and 75 to be consistent with how age was considered by the studies. For penetrance of *BRCA* mutations when a positive family history is present,

$$P(D^+ \mid G, FH) = \frac{P(G \mid D^+, FH)P(D^+ \mid FH)}{P(G \mid D^+, FH)P(D^+ \mid FH) + P(G \mid D^-, FH)P(D^- \mid FH)}. \quad (5)$$

We conducted a sensitivity analysis in the average and moderate risk groups by calculating penetrance two ways by including and excluding studies of women with family history of breast or ovarian cancer. Calculation of 95% CI for penetrance in (4) and (5) is similar to that described above, with appropriate substitution of terms.

Appendix E. Search and Selection of Literature



ELSI: ethical, legal, and social implications

Appendix F. Reviewers

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Appendix G. Evidence Table of Genetic Counseling Studies

Author, year	Purpose	N	Population / Setting	Inclusion / Exclusion criteria
Bowen et al, 2004[38]	To test the effects of two types of breast cancer risk counseling (group psychosocial or individual genetic) on perceived risk, negative affect, and worry about breast cancer	799	Recruitment from among family members with breast cancer and through notices in local electronic and print outlets. Recruitment completed in 8 months. Women with a range of actual breast cancer risk levels were included.	Inclusion: 1. women aged 18-74 2. at least one relative with breast cancer 3. no personal history of breast or ovarian cancer 4. no family history consistent with a *BRCA* mutation for breast cancer risk 5. living within 60 mile radius of research center 6. willingness to complete research activities 7. completed and returned baseline questionnaire
Bowen et al, 2002[39]	To test the effects of breast cancer risk on interest in genetic testing in women who have a family history of breast cancer	721	Women recruited from the Seattle area--see Bowen et al, 1999.[243] All volunteered after seeing a notice, hearing about the study from a network or through a relative with cancer.	Inclusion: 1. women aged 18-74 2. lived within 60 miles of research center 3. agreed to participate in counseling & complete questionnaires 4. at least 1 relative affected by breast cancer Exclusion: more than 1 close relative affected by breast cancer

Appendix G. Evidence Table of Genetic Counseling Studies

Author, year	Family history / Risk level definition	Interventions
Bowen et al, 2004[38]	Family history: Self-report of any family history of breast cancer Risk level: Calculated by use of Gail and Claus models, along with population data	Telephone screening survey to determine eligibility, followed by mailed baseline survey. Those who returned completed surveys were randomized to individual genetic counseling (IGC), group psychosocial counseling (PC), or a delayed intervention control group. ICG: Telephone contact with genetic counselor to review pedigree information. One 2-hour session following protocol based on standard genetic practice. Letter sent to participant within 2 weeks summarizing the session. PC: Group of 4-6 participants met for four, 2-hour sessions led by a trained health counselor. Each participant received her own risk assessment sheet, personalizing the group discussion to her own risk status. Main topics: risk assessment and perception, screening, stress management and problem solving, and social support. For ICG and PC, brief survey on reactions to counseling within 4 weeks of last counseling contact. Mailed 2nd assessment 6 months after randomization, with a reminder call and offer of phone completion to those who did not return survey after 2 weeks.
Bowen et al, 2002[39]	Family history: Close relatives affected by breast cancer included grandmothers, mothers, sisters, and aunts Risk level: Gail and Claus scores, along with population data	Telephone screening survey to determine eligibility, followed by mailed baseline survey. Those who completed survey randomly assigned to individual genetic counseling (IGC), psychosocial group counseling (PGC) or control group (CG). Mailed follow-up survey 6 months after randomization. IGC: Phone call to review pedigree information followed by a single 2-hour counseling session. Subject given information on her own risk for breast cancer using Gail and Claus scores along with population data. Information given on genetic testing, current knowledge about nonhereditary risk factors, and current screening techniques. Summary letter provided. PGC: Four, 2-hour group meetings with 4-6 women led by a health counselor. Included: risk assessment and perception, education, stress management, problem-solving and social support. Personal risk for breast cancer, interpretation and appropriate screening provided privately to subjects. CG: Offered choice of counseling modality after the final follow-up.

Appendix G. Evidence Table of Genetic Counseling Studies

Author, year	Results
Bowen et al, 2004[38]	Perceived risk decreased by 50% for participants in the two counseling groups relative to control ($p<0.01$). Cancer worry decreased in both counseling groups by one scale point ($p<0.05$). There were no differential effects of counseling type on perceived risk or cancer worry. Those in the PC group reported more anxiety change than those in the other groups. Depression was not impacted by study group.
Bowen et al, 2002[39]	Counseling about breast cancer risk slightly changed level of interest in genetic testing for breast cancer risk in women with a family history. Those who participated in counseling were less interested in genetic testing and less likely to view themselves as good candidates. Stigma and access beliefs about genetic testing were related to the effect of counseling on candidacy judgment. As women gained more information, they were less likely to want to participate in testing.

Appendix G. Evidence Table of Genetic Counseling Studies

Author, year	Purpose	N	Population / Setting	Inclusion / Exclusion criteria
Burke et al, 2000[40]	To assess whether modified traditional genetic counseling causes women with an intermediate risk of breast cancer to have a more realistic view of their risk, of genetic testing, and to decrease breast cancer worry	793	Sources for solicitation include women who live within 60 miles of Seattle: 2 studies at Fred Hutchinson Cancer Research Center, an oncologist's practice at University of Washington, mass media announcements.	Inclusion: 1. between 18-74 years old 2. lives within 60 miles of Seattle 3. has at least 1 biological relative who has been diagnosed with breast cancer Exclusion: 1. has personal history of breast or ovarian cancer 2. has family history indicative of autosomal dominant inheritance of breast cancer
Cull et al, 1998[41]	To evaluate use of video for education on the genetic basis of breast cancer and on strategies for breast cancer risk management in a breast cancer family clinic	159	A consecutive series of women newly referred to the breast cancer family clinic were invited by mail to participate. 24% of the video before (VB) and 30% of the video after (VA) group were referred by another hospital clinic. One subject in each group had been referred from another genetic clinic. The remaining were referred by general practitioners.	None reported

Appendix G. Evidence Table of Genetic Counseling Studies

Author, year	Family history / Risk level definition	Interventions
Burke et al, 2000[40]	Intermediate family history of breast cancer: 1 or more biological relative(s) with breast cancer but whose pedigree suggests a low likelihood of autosomal dominant transmission. Family history indicative of autosomal dominant inheritance of breast cancer: 2 or more 1st degree or one 1st degree and one 2nd degree relative with either breast cancer before age 50 or ovarian cancer at any age, or at least 2 paternal 2nd degree relatives with either breast cancer before age 50 or ovarian cancer at any age. The Claus model showed that these women would have at least a 20% breast cancer risk by age 79.	Random assignment to 3 groups: individual genetic counseling (120 women), psychosocial group counseling (113 women), control (123 women). Psychosocial group counseling details not included in this paper. Adapted genetic counseling protocol for women with intermediate risk included pre-counseling telephone call, baseline questionnaire, individual genetic counseling session, immediate follow-up questionnaire, 6-month follow-up questionnaire, mailed summary letter.
Cull et al, 1998[41]	Not reported	Subjects sent information about study with initial clinic appointment 4 weeks before the appointment. They were asked to return baseline questionnaires and forms within 2 weeks if wanting to participate. Those who did so were randomized either to the VB group, and were sent a copy of the educational video about 10 days before the clinic consultation, or to the VA group, taking the video home after the post-clinic assessment. Clinic consultation: individual meeting with geneticist to discuss individual risk and with breast surgeon to discuss risk management. Clinicians noted session length and rated assessment of it. Post-clinic assessment included completion of instruments. Follow-up assessment by mail 4 weeks later.

Appendix G. Evidence Table of Genetic Counseling Studies

Author, year	Results
Burke et al, 2000[40]	Significant differences between counseling and control groups in mean perceived risk of breast cancer (F=27.9, p<0.009). Significant differences over time in perceived risk for the counseling group (F=65.9, p<0.001). Interaction between group and time for perceived risk was significant (F=50.6, p<0.001). Low over-estimators of breast cancer risk reduced risk estimates by an average of 19 percentage points after counseling, compared with high over-estimators who reduced risk estimates by an average of 36 percentage points (F=13.41, p<0.00001). After counseling, those who perceived themselves as candidates for testing decreased from 82% to 60% and interest in testing was reduced from 91% to 60%. 82 (70%) liked the counseling very much. 65 (56%) found the counseling very useful and 26 (22%) found it moderately useful. After receiving risk estimates, 39 (33%) were a lot less worried and 37 (32%) were a little less worried.
Cull et al, 1998[41]	Duration of Consultation: VB group spent less time with surgeon (mean 11.8 min vs 14.6, p< 0.05), but their time with geneticist was not significantly shorter. Risk Assessment: No significant difference between VB or VA in accuracy of estimate at baseline. VB retained accuracy from clinic to follow-up. VA were more likely to underestimate at follow-up (p< 0.05). Understanding of Risk Information: Subjective: At baseline and at follow-up, no significant difference. Objective: VB had higher scores (p< 0.01) and a higher proportion of correct responses to more items. Follow-up: no significant differences after adjusting for education level (t =0.34). Emotional Distress: No significant difference in groups in anxiety or distress levels. Use of Video and Family Discussion: VB: 94% watched video at least 1x from start to finish. 76% reported it offered new information. VA: 41/42 who gave follow-up data watched the video at least once and 41% of them said it gave new information. In both VA and VB, most (66% and 65%, respectively) watched it alone and most discussed it with a partner.

Appendix G. Evidence Table of Genetic Counseling Studies

Author, year	Purpose	N	Population / Setting	Inclusion / Exclusion criteria
Green et al, 2004[120]	To compare effectiveness of a computer-based decision aid with standard genetic counseling in educating women about genetic testing for *BRCA1* and *BRCA2*	211	Subjects were enrolled from outpatient clinics at 6 US medical centers offering cancer genetic counseling for women with personal or family histories of breast cancer.	Inclusion: 1. referred for genetic counseling for evaluation of personal or family history of breast cancer 2. able to read, write, and speak English Exclusion: 1. previous genetic counseling or testing for inherited breast cancer susceptibility
Lerman et al, 1999[42]	To investigate racial differences in response to two alternate pretest education strategies for *BRCA1* genetic testing: a standard education model and an education plus counseling model	581	Subjects were recruited from two cancer centers (Georgetown University Medical Center or Washington Hospital Center).	Inclusion: Caucasian and African American women with a family history of breast cancer or ovarian cancer Exclusion: personal history of cancer (except basal cell or squamous cell skin cancers)

Appendix G. Evidence Table of Genetic Counseling Studies

Author, year	Family history / Risk level definition	Interventions
Green et al, 2004[120]	Low risk: less than 10% chance of carrying a deleterious *BRCA1* or *BRCA2* mutation defined by BRCAPRO model High risk: 10% or higher chance of carrying deleterious *BRCA1* or *BRCA2* mutation defined by BRCAPRO model	Separate computer-generated randomization lists for low-risk and high-risk individuals at each study site. Randomized to counselor group or interactive computer-based educational program. Baseline questionnaire completed on or just before the day of first appointment. Assessments at 1 and 6 months after study visit. 1. Counseling group: standard topics covered that were consistent with current practice guidelines and with information presented in the computer program. Individualized risk estimates provided on likelihood of carrying a genetic mutation and of developing breast cancer. Psychosocial component included to address emotional concerns if presented. 2. Computer-based education program: interactive, multimedia CD-ROM-based decision aid designed to educate women about breast cancer, heredity, and benetfits and limitations of genetic testing. Self-paced and user-driven. Participants used for an average of 45-60 minutes, and then completed post-intervention measures, followed by counseling.
Lerman et al, 1999[42]	At least one 1st degree relative affected with breast cancer and/or ovarian cancer	Randomly assigned by computer to control group (wait list control), education only group, or education + counseling group at the end of baseline telephone interview. 1. Baseline phone interview for demographic information. 2. Education only: topics discussed included individual risk factors for breast cancer and ovarian cancer and patterns of inheritance for breast and ovarian cancer susceptibility. Subjects given qualitative estimates of their risk of developing breast cancer and ovarian cancer. Pedigrees were reviewed. Potential benefits, limitations, and risks of genetic testing for inherited breast cancer and ovarian cancer susceptibility also reviewed. 3. Education + counseling: provided the same education and materials described above. Subjects guided through a set of questions that explored personal issues related to cancer and genetic testing. Subjects discussed the emotional impact of having a family history of cancer, psychosocial implications of genetic testing for inherited breast cancer and ovarian cancer susceptibility, anticipated reactions to a positive and negative test result, and intentions to communicate test results to family members and friends.

Appendix G. Evidence Table of Genetic Counseling Studies

Author, year	Results
Green et al, 2004[120]	Knowledge: Both genetic counseling and the computer-based education program increased knowledge scores, regardless of risk status (p<0.001). Change in knowledge was greater in the computer group among women at low risk of carrying a mutation (p=0.03). Anxiety: Mean state anxiety scores were within normal range for both groups at baseline and after either intervention, regardless of risk status. The counseling group had lower anxiety scores post-treatment (p=0.001). Anxiety scores did not change significantly after using the computer-based program, but were lower after use of both counseling and the computer-based program. Risk perception: Perception of absolute risk of breast cancer decreased after either intervention among all participants (p<0.001). Absolute breast cancer risk perception was lower after using the computer-based program (p=0.006). For low-risk women, genetic risk perception was lower after counseling in both interventions (p<0.001). Genetic testing intention: Intention to participate in testing decreased after either intervention for low-risk but not high-risk women (p<0.001 after counseling, p<0.05 after computer-based education). Decision satisfaction: The counseling group had lower mean scores on a decisional conflict scale (p=0.04), and low-risk women, higher mean scores on a satisfaction-with-decision scale (p=0.001).
Lerman et al, 1999[42]	Overall: African American women were found to differ significantly from Caucasian women in the effects of the interventions on testing intentions and provision of a blood sample. Effects were independent of socioeconomic status and referral mechanism. Genetic testing intention: Family history and baseline genetic testing intentions both made significant independent contributions to 1-month genetic testing intentions. Women with stronger family history of cancer had greater increases in intentions. Only in African American, education + counseling led to greater increases in intentions than education only (p=0.003). IES scores: All groups evidenced a reduction in distress from baseline to 1 month. However, this decrease, although not a significant difference, was smallest among African American women who received education + counseling.

Appendix G. Evidence Table of Genetic Counseling Studies

Author, year	Purpose	N	Population / Setting	Inclusion / Exclusion criteria
Lerman et al, 1996[43]	To evaluate the impact of individualized breast cancer risk counseling among women with a family history of breast cancer	239	Subjects were sisters, daughters, and/or mothers of women under treatment for breast cancer at a cancer treatment center.	Inclusion: women aged 35 and older living within a 6-hour drive of the clinic with a positive history of breast cancer in at least one first-degree relative Exclusion: prior diagnosis of cancer (except basal or squamous cell skin cancers)
Lerman et al, 1995[44]	To study effect of individualized breast cancer risk counseling	438	Subjects identified by relatives under treatment for breast cancer at either Fox Chase Cancer Center or Duke Comprehensive Cancer Center.	Inclusion: 1. women aged 35 and older 2. family history of breast cancer Exclusion: 1. personal history of cancer 2. younger than 35
Lobb et al, 2002[118]	To assess with validated measures of psychological outcome, the use of an audiotape in genetic counseling in a large sample of affected and unaffected women attending a familial cancer clinic	244	Consecutive women attending any one of 10 familial cancer clinics in four Australian states. Quota sampling used to balance sample between affected and unaffected women.	Exclusion: 1. unable to give informed consent 2. evidence of severe mental illness 3. limited literacy in English 4. younger than age 18

Appendix G. Evidence Table of Genetic Counseling Studies

Author, year	Family history / Risk level definition	Interventions
Lerman et al, 1996[43]	Family history: At least one 1st degree relative with breast cancer Risk level: Based on Gail model	Women in treatment for breast cancer identified sisters, daughters, and/or mothers who were then sent an introduction letter. All who did not decline by phone participated 2 weeks later in a phone interview baseline assessment of demographics, risk factors, coping styles, and distress. Completers were given information about the study and were asked to participate. They were randomized to Individualized Breast Cancer Risk Counseling (BCRC) or General Health Counseling (GHE), the control condition. Immediately before the 1-hour intervention, participants completed self-report questionnaires. After 3 months, a follow-up phone interview assessed risk perceptions and screening practices. Participants were then asked to complete a set of self-report questionnaires.
Lerman et al, 1995[44]	At least one 1st degree relative with breast cancer Breast cancer risk estimates for individual women were calculated using subject's Gail model variables and estimated the lifetime probability of developing breast cancer, the 95% CIs, and the estimated lifetime risk for a woman of the same age with the lowest risk of disease.	Randomized to control group (genetic health counseling) or study group (breast cancer risk counseling) Study group: 1) discussion of individual factors contributing to elevated risk, 2) presentation of individualized risk data, 3) recommendations for annual mammography and clinical breast exams, 4) instruction in breast self-exam Control group: 1) interview assessment of current health practices, 2) age-specific recommendations for variety of cancer screening tests, 3) encouragement to quit smoking, 4) suggestions for reducing dietary fat to 30% or less, 5) recommendations for regular aerobic exercise
Lobb et al, 2002[118]	Number of 1st and 2nd degree relatives who had developed breast or ovarian cancer at baseline	Women invited to participate when they telephoned familial cancer clinic to make an appointment. Women were asked to complete mailed baseline questionnaire sent 2 weeks before clinic appointment. Double-blind randomization occurred in clinic immediately after the genetic counseling. All counseling sessions were audiotaped and women were then randomized to receive the audiotape (T group) or not (NT group). Follow-up questionnaire mailed 3 weeks after counseling.

Appendix G. Evidence Table of Genetic Counseling Studies

Author, year	Results
Lerman et al, 1996[43]	After controlling for education level, women who received BCRC had significantly less breast cancer specific distress at 3-month follow-up compared with those in the control (GHE) group ($p<0.01$). There was no difference between the groups in general distress. Psychological benefits of BCRC were greater for women with less formal education ($p<0.01$). In both groups, women with monitoring coping styles had increased general distress from baseline to follow-up ($p<0.01$).
Lerman et al, 1995[44]	Breast cancer preoccupation: IES average score on measure of breast cancer preoccupation was 6.9+ 0.71 (means +SE). No significant baseline difference in risk comprehension between groups; however, significant change in risk comprehension at 3-month follow-up due to movement in risk-counseling group from overestimation to accurate or underestimation.
Lobb et al, 2002[118]	In the T group, affected women ($p = 0.03$) and women with increased generalized anxiety at baseline ($p = 0.01$) were significantly more likely to listen to the tape. Women who were more depressed ($p = 0.06$) and with lower breast cancer genetics knowledge ($p = 0.07$) were more likely to listen to the tape. Unaffected women in the T group were less likely to be accurate in their risk perception at follow-up ($p = 0.05$) than unaffected women in the NT group. The tape had no effect on risk accuracy when analysis included only those inaccurate at baseline. There was a trend for those in the T group to have improved scores on depression at follow-up ($p = 0.06$). In a repeated analysis with only those who listened to the tape, those in the T group had more anxiety reduction ($p = 0.02$) and more depression reduction ($p = 0.01$). Coping style (monitoring vs. blunting) did not influence likelihood of listening to the tape or response to the tape.

Appendix G. Evidence Table of Genetic Counseling Studies

Author, year	Purpose	N	Population / Setting	Inclusion / Exclusion criteria
Watson et al, 1998[119]	To look at recall of risk information after genetic counseling, and to determine impact of receiving an audiotape of the genetic consultation on level of recall, cancer-related worry, and uptake of risk management methods	135	First time attendees at the cancer family clinics of 2 London hospitals--Royal Marsden, Sutton and London, and St. George's Hospitals.	Inclusion: 1. women with a family history of breast cancer 2. first visit to genetic clinic 3. never having been clinically affected with cancer 4. no known mental illness 5. aged 18 or over

Appendix G. Evidence Table of Genetic Counseling Studies

Author, year	Family history / Risk level definition	Interventions
Watson et al, 1998[119]	Not reported	Randomized to consultation plus audiotape (n=60) or consultation only (n=55) (randomized at clinic immediately after consultation to minimize bias). All subjects were referred for genetic counseling with a clinical geneticist who provided a consultation, including pedigree based on risk calculation and information regarding management options based on risk level. All were offered instructions on self-exam and clinical exam as part of consultation. In addition to consultation, the case group received an audiotape of the consultation.

Appendix G. Evidence Table of Genetic Counseling Studies

Author, year	Results
Watson et al, 1998[119]	Overall: GHQ-12 scores: For combined groups, median score was 1 (range 0-11). 36 subjects had a score indicative of psychological morbidity (>3) at baseline and 31 at 1-month and 6-month follow-ups. CWS scores: For both groups median score was 11 (range 6-22). CI=10-12 for cases and CI=10-11 for controls; mean 11.14 (SD 3.23) for cases and mean 11.39 (SD 3.37) for controls. Scores fell in subjects given a tape of consultation from median 11 at baseline to 10 at 1 month, then 9 at 6 months. Relative risk scores: At 1-month follow-up 41% accurately recalled their risk of developing cancer, 25% overestimated, 11% underestimated, 23% didn't know/didn't remember. Results suggest that risk figure, regardless of accuracy, doesn't reflect more general view about risk compared with average women. Risk figure given as odds ratio compared with other formats (percentage or descriptive terms): odds ratio--71% were accurate in recall compared with 25% when given in other formats. Risk questionnaire scores: Usefulness of information rated on a visual analog scale. Average ratings were high, ranging from 8.5 (population risk) to 9.1 (risk of gene in family). Risk of gene in family, lifetime risk, and risk < age 50 were rated significantly more useful than population risk, risk of no cancer by age 50, and risk of disease over next 5 years. Medical management uptake: No significant correlation between cancer worry change scores and either level of breast clinical exam (p=0.8) or mammography (p=0.8), no difference between cases and controls for rate of self-exam, doctor exam, or mammography at 6-month follow-up, no difference between groups for other health behaviors unaffected by whether consultation tape was received or not.

CWS, Cancer Worry Scale; GHQ-12, General Health Questionnaire (12-item); IES, Impact of Events Scale.

Appendix H. Quality Ratings of Genetic Counseling Studies

Author, year	Study Design	Random assignment?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Blinding: outcome assessors, care provider, patient?	Intention-to-treat analysis?	Maintenance of comparable groups?
Bowen et al, 2004[38]	RCT	Yes	Yes	Yes	Yes	N/A	NR	Yes
Bowen et al, 2002[39]	RCT	Yes	NR	Yes	Yes	N/A	No	Yes
Burke et al, 2000[40]	RCT	Yes	NR	Yes	Yes	N/A	NR	Yes
Cull et al, 1998[41]	RCT	Yes	Yes	Yes	Yes	N/A	NR	Yes
Green et al, 2004[120]	RCT	Yes	N/A	Yes	Yes	N/A	NR	Yes
Lerman et al, 1999[42]	RCT	Yes	NR	Yes	Yes	N/A	NR	No
Lerman et al, 1996[43]	RCT	Yes	NR	Yes	Yes	Outcome assessors blind only	NR	Yes
Lerman et al, 1995[44]	RCT	Yes	NR	Yes	Yes	Outcome assessors blind only	No	Yes
Lobb et al, 2002[118]	RCT	Yes	Yes	Yes	Yes	N/A	Yes	Yes
Watson et al, 1998[119]	RCT	Yes	Yes	Yes	Yes	N/A	Yes	Yes

Appendix H. Quality Ratings of Genetic Counseling Studies

Author, year	Reporting of attrition, contamination, etc.?	Differential loss to follow-up or overall high loss to follow-up?	Quality rating	External validity
Bowen et al, 2004[38]	Yes	1% loss genetic counseling 4% loss psychosocial counseling 1% loss control	Fair	Women in general public with breast cancer
Bowen et al, 2002[39]	Yes	8% loss psychosocial counseling 10% loss genetic counseling 10% loss control	Fair	Women in Seattle area with lower risk of breast cancer
Burke et al, 2000[40]	Yes	3% loss counseling 8% loss control	Fair	Women in Seattle area with intermediate family history of breast cancer
Cull et al, 1998[41]	Yes	24% loss video 37% loss control	Good	Women from 4 Scottish cancer family clinics
Green et al, 2004[120]	Yes	26% loss overall at 6 month follow-up	Good	Women from 6 U.S. medical center clinics offering genetic counseling
Lerman et al, 1999[42]	Yes	49% loss overall (32% loss Causasian; 51% loss African American)	Fair	Georgetown University Medical Center and Washington Hospital Center
Lerman et al, 1996[43]	Yes	12% loss overall 3-month telephone survey 37% loss overall 3-month mail survey	Fair	Cancer treatment centers
Lerman et al, 1995[44]	Yes	12% loss overall	Fair	Fox Chase Cancer Center and Duke Comprehensive Cancer Center
Lobb et al, 2002[118]	Yes	18% loss overall	Good	10 familial cancer clinics in 4 Australian states
Watson et al, 1998[119]	Yes	7% loss overall 1-month follow-up 21% loss overall 6-month follow-up	Good	Women with a family history of breast cancer attending two London genetic clinics

NR, not reported; RCT, randomized controlled trial.

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Abeliovich et al, 1997[152] *The founder mutations 185delAG and 5382insC in BRCA1and 6174delT in BRCA2 appear in 60% of ovarian cancer and 30% of early-onset breast cancer patients among Ashkenazi women*	Prev-CA		High-risk breast cancer or genetics clinic	Breast cancer: prevalent Ovarian cancer: prevalent if incident	Inclusion: Jewish women with breast and/or ovarian cancer referred from outpatient oncology clinic or oncogenetic counseling clinic
Anglian Breast Cancer Study Group, 2000[27] *Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases*	Pen & Prev-CA	Anglian Breast Cancer Study Group	Cancer registry	Breast cancer: prevalent Other: Pedigrees of breast cancer probands	Inclusion: 1. women 2. diagnosed < 55 years of age 3. diagnosed 1/1/1991 - 6/30/1996, alive 7/1/1996

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Abeliovich et al, 1997[152] *The founder mutations 185delAG and 5382insC in BRCA1and 6174delT in BRCA2 appear in 60% of ovarian cancer and 30% of early-onset breast cancer patients among Ashkenazi women*	Israel	Ashkenazi Jewish (199) and non-Ashkenazi Jewish (44)	Case series	Prevalence	Definite positive family history: 3 or more 1st degree relatives with breast and/or ovarian cancer. At least one 1st-, 2nd-, or 3rd-degree female relative with breast or ovarian cancer.	243
Anglian Breast Cancer Study Group, 2000[27] *Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases*	UK, East Anglia	Unselected	Case series: prevalence Families: penetrance	Prevalence Actual risk: method for calculating risk: home-grown methods applied to family data Relative risk: comparison group for relative risk: population rates	N/A	Individuals: 1,435 Families: 23

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Abeliovich et al, 1997[152] *The founder mutations 185delAG and 5382insC in BRCA1and 6174delT in BRCA2 appear in 60% of ovarian cancer and 30% of early-onset breast cancer patients among Ashkenazi women*	Not reported	*BRCA1* and *BRCA2*	Ashkenazi Jewish panel	Blood	N/A	82% Ashkenazi Jewish 18% non-Ashkenazi Jewish
Anglian Breast Cancer Study Group, 2000[27] *Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases*	Group description: breast cancer cases Participation rate: 71% contacted, 51% total group 2,805 eligible 569 died 200 MD refused 2,028 contacted 1,435 blood sample 85% amplified OK > 1,220 effective sample size	*BRCA1* and *BRCA2*	Screening with confirmation by sequencing: MHA	Blood	Entire coding region Intron-exon boundaries	Age: not specified Gender: 100% women Race/ethnicity: not specified

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Abeliovich et al, 1997[152] *The founder mutations 185delAG and 5382insC in BRCA1and 6174delT in BRCA2 appear in 60% of ovarian cancer and 30% of early-onset breast cancer patients among Ashkenazi women*	Mutation prevalence for Ashkenazi Jewish women with ovarian cancer is 62%, with breast cancer diagnosed <40 is 30%, with breast cancer diagnosed >40 is 10%.	Cancer is verified, presumably. Ashkenazi Jewish founder mutation only Clinic--"most" agreed, referrals from one genetic clinic Prevalent cases--possible bias	Ashkenazi Jewish founder mutations
Anglian Breast Cancer Study Group, 2000[27] *Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases*	Mutations in *BRCA1/BRCA2* are rare in the population and account for a small proportion of breast cancer. Account for less than 1/5 of familial breast cancer risk.	Cancer verified: yes, probands; proband report, relatives Completeness of mutation identification: estimated 63% sensitivity Evidence of bias: relatives of younger-onset cases	Predicted to encode a truncated protein

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Anton-Culver et al, 2000[144] *Characteristics of BRCA1 mutations in a population-based case series of breast and ovarian cancer*	Prev-CA		Cancer registry (probands)	Breast cancer: incident Ovarian cancer: incident	Inclusion: 1. men & women, USA, unselected 2. all breast cancer cases aged 18+ diagnosed in Orange County, CA, from 3/1/94 to 3/1/95 and all ovarian cancer cases diagnosed 3/1/94 to 3/1/95. 3. Probands from Cancer Surveillance Program of Orange County (CSPOC) cancer registry.
Antoniou et al, 2002[28] *A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes*	Pen & Prev-CA	Anglian Breast Cancer (ABC) Study Multiple case families (B families)	Cancer registry (ABC Study) Referred families (B)	Breast cancer: prevalent (ABC Study) Other: pedigrees of breast cancer probands Family history of breast and/or ovarian cancer (B)	See Anglian Breast Cancer Study Group, 2002 Inclusion: 2 or more breast cancer cases (1 diagnosed <50)

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Anton-Culver et al, 2000[144] *Characteristics of BRCA1 mutations in a population-based case series of breast and ovarian cancer*	USA	Unselected	Case series	Prevalence	Family history: 1 or more 1st degree relative with breast or ovarian cancer or 2 or more 2nd degree relatives with breast or ovarian cancer on the same side of the family.	2,030 probands: 342 ovarian cancer, 17 male breast cancer, 1,671 female breast cancer cases. 362 breast and 70 ovarian cancer patients refused to participate.
Antoniou et al, 2002[28] *A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes*	UK	Unselected	Case series (ABC) Convenience sample (B)	Prevalence	Not reported	1,484 cases and 156 families

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Anton-Culver et al, 2000[144] *Characteristics of BRCA1 mutations in a population-based case series of breast and ovarian cancer*	Ovarian cancer: 272/342 (79.5%) Female breast cancer: 1,310/1,671 (82%) Male breast cancer: 16/17 (94.1%)	*BRCA1*	Selected mutations: breast cancer, 7 mutations Screening only: breast cancer for above mutations, Allele-specific oligonucleotide (ASO); ovarian cancer: RNase mismatch cleavage assay	Blood	N/A	673 female breast cancer probands, 120 ovarian cancer probands. 29% of breast and 38% of ovarian cancer probands under age 50 at diagnosis. 9 breast cancer probands were male. 4.5% of breast and 3.3% of ovarian cancer probands were Ashkenazi Jewish. Mean age for breast cancer cases: 58.4 Mean age for ovarian cancer cases: 55.3
Antoniou et al, 2002[28] *A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes*	Not reported	*BRCA1* and *BRCA2*	Screening with confirmation by sequencing: CSGE	Blood	Entire coding region Intron-exon boundaries (see Anglian Breast Cancer Study Group, 2000)	Not reported

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Anton-Culver et al, 2000[144] *Characteristics of BRCA1 mutations in a population-based case series of breast and ovarian cancer*	*BRCA1* mutation prevalence: 1.6% (0.8-2.9) for females with breast cancer and 3.3% (0.8-8.3) for ovarian cancer cases. No mutations were found among non-white cases. Positive family history of breast or ovarian cancer is significantly associated with *BRCA1* mutation status among breast and ovarian cancer probands.	Cancer was verified through pathology report, clinical record, death certificate, interview with 2nd relative; pathology review breast/ovarian cancer 100% probands, 76% 1st-degree, 65% 2nd-degree	Ashkenazi Jewish founder mutations; *BRCA1* - R841W, int5-IIT-G, 2594delC, 3600del-AAGATACTAGT, 962delCTCA
Antoniou et al, 2002[28] *A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes*	ABC: 8 (0.5%) *BRCA1* and 15 (1.0%) *BRCA2* mutations B: 21 (13.5%) *BRCA1* and 18 (11.5%) *BRCA2* mutations among index cases	Was not clear if B group's cancer was verified. Screening with sequencing. B: referral, volunteer. Evidence of bias with prevalent cases.	Thought to be disease-causing, not otherwise specified

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Antoniou et al, 2003[130] *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*	Pen		Other: meta-analysis	Breast cancer: prevalent and incident Ovarian cancer: prevalent and incident	Inclusion: 1. women 2. men 3. age at diagnosis: varied by study 4. enumeration of all 1st degree relatives of identified mutation carriers
Boyd et al, 2000[154] *Clinicopathologic features of BRCA-linked and sporadic ovarian cancer*	Prev-CA		Comprehensive cancer center	Ovarian cancer: incident	Inclusion: 1. ovarian cancer diagnosed 2. treated at specific cancer center 3. diagnosed between December 1986 and August 1998 4. Jewish origin 5. women

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Antoniou et al, 2003[130] *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*	USA, Australia, Canada, Israel, Finland, Hungary, Hong Kong, Iceland, Italy, Poland, Sweden, UK	Selection varies by study	Families	Actual risk: method for calculating risk: segregation analysis of family data	N/A	280 families of *BRCA1* + 218 families of *BRCA2* +
Boyd et al, 2000[154] *Clinicopathologic features of BRCA-linked and sporadic ovarian cancer*	USA	Jewish origin	Case series	Prevalence	N/A	189

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Antoniou et al, 2003[130] *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*	Varied by study Approximate range: 25-80%	*BRCA1* and *BRCA2*	Varied by study From ethnic-specific testing to sequencing	Blood	Varied by study	Age: not specified (some studies included only the families of early-onset breast cancer cases) Gender: not specified (3 studies included male breast cancer cases); risks are calculated for women Race/ethnicity: varied by study
Boyd et al, 2000[154] *Clinicopathologic features of BRCA-linked and sporadic ovarian cancer*	N/A	*BRCA1* and *BRCA2*	Selected mutations: Ashkenazi Jewish panel All mutations confirmed as germline through analysis of DNA from non-tumor tissue	Tissue specimen	N/A	100% women of Jewish origin. Mean age at diagnosis for *BRCA1* cases = 54 years (SD 11) (n=67). Mean age at diagnosis for *BRCA2* cases = 62 years (SD 10) (n=21). Mean age at diagnosis for sporadic, nonhereditary cases = 63 years (SD 12) (n=101)

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Antoniou et al, 2003[130] *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*	Pattern of risks similar to those in multiple-case families, but absolute magnitudes were lower, especially for *BRCA2.* Risks in carriers were higher among relatives of breast cancer cases diagnosed at < 35 years.	Estimated risks higher because estimates are from relatives of individuals diagnosed with breast cancer. Cancer diagnoses in relatives confirmed in some studies, but not others. Techniques for mutation detection varied widely. Analyses assume Mendelian segregation of the mutation.	"Pathogenic" according to generally accepted criteria (BIC website): frame shift or nonsense mutations, splice site mutations predicted to cause aberrant splicing, large deletions or duplications, and miss sense mutations classified as such by BIC (included only mutations in the ring-finger domain of *BRCA1*)
Boyd et al, 2000[154] *Clinicopathologic features of BRCA-linked and sporadic ovarian cancer*	Age at ovarian cancer diagnosis is younger in *BRCA1* and *BRCA2* mutation carriers. Age at diagnosis for *BRCA2* mutation carriers is similar to non-carriers. Mutation frequency: *BRCA1*: 35% *BRCA2*: 11%	Cancer was verified. Ashkenazi Jewish panel only. Tissue was available for all subjects. National Cancer Institute (NCI) comprehensive cancer center may have more advanced and complicated cases. Survival in noncarriers is comparable to that for participants in clinical trials.	Ashkenazi Jewish founder mutations

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Brose et al, 2002[21] *Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program*	Pen	University of Michigan, University of Pennsylvania	High-risk breast cancer clinic or genetics clinic	Families seeking breast cancer risk counseling with documented deleterious *BRCA* mutations in family Breast cancer risk assessment clinics	Inclusion: Documented deleterious *BRCA1* mutation in family
Couch et al, 1997[36] *BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer*	Prev-CA		High-risk breast cancer clinic	Breast cancer: prevalent	Inclusion: Women with breast cancer. Familial risk factor for breast cancer or diagnosis before age 40

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Brose et al, 2002[21] *Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program*	USA	Unselected	Families	Actual risk: method for calculating risk: home-grown method applied to family data Relative risk: comparison group: population rates	N/A	147 families
Couch et al, 1997[36] *BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer*	USA	Unselected	Case series	Prevalence	Family history: 1 to 11 cases of breast cancer per family	263

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Brose et al, 2002[21] *Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program*	Not relevant	*BRCA1*	Clinical testing Includes presumed carriers	Blood	Not stated	Gender and ages: Women ≤ 30 3%, 31-40 15%, 41-50 28%, 51-60 24%, 61-70 15%, >70 14%. Men < 30 3%, 31-40 10%, 41-50 17%, 51-60 20%, 61-70 17%, >70 34%. Race/Ethnicity: Caucasian 95%, African American, Asian, Native American 5%
Couch et al, 1997[36] *BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer*	No patient refused to participate in the study	*BRCA1*	Screening with confirmation by sequencing: CSGE exons 2,3 & 5-24	Blood	Entire coding region Intron-exon boundaries	For 169 women with familial risk factors: Mean age at diagnosis in families: <35 - 39% 35-39 - 16% 40-44 - 19% 45-49 - 14% 50-54 - 20% 55-59 - 14% ≥60 - 14% 94 women diagnosed before 40 years of age

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Brose et al, 2002[21] *Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program*	Cancer risk estimates higher than in population-based studies, and lower than in linkage studies. May better represent risks for those identified in risk evaluation clinics.	Cancer verified: not stated Completeness of mutation identification: presumably excellent--clinical testing Participation rate: N/A Evidence of bias: intentional referral population, no consideration of prophylactic surgeries, missing data--excluded individuals	Ashkenazi Jewish founder mutations; others judged to be clinically significant as part of clinical testing
Couch et al, 1997[36] *BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer*	*BRCA1* mutation frequency: 16% family history of breast cancer 7% family history of breast cancer but no ovarian cancer 13% breast cancer diagnosed <40 years old Even in women from high-risk families, the majority of *BRCA1* mutation test results will be negative and therefore uninformative.	Cancer is presumably verified. 95-99% sensitivity Representative of patients seen in referral clinics for inherited breast cancer risk	Ashkenazi Jewish founder mutations; other mutations not specified

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Eccles et al, 1998[141] *BRCA1 mutations in southern England*	Prev-CA		High-risk breast cancer clinic or genetics clinic	Breast cancer Family history or breast and/or ovarian cancer	Inclusion: 1. women 2. for Group 1: Diagnosed < 40 years 3. for Group 2: Bilateral breast cancer diagnosed ≥ 40 years 4. for Group 3: Strong family history of breast/ovarian cancer and DNA sample available from affected relative
FitzGerald et al, 1996[150] *Germ-line BRCA1 mutations in Jewish and non-Jewish women with early-onset breast cancer*	Prev-CA		Breast cancer referral centers	Breast cancer: prevalent	Inclusion: Women diagnosed with breast cancer at or before age 40 between 1981 and 1992
Fodor et al, 1998[125] *Frequency and carrier risk associated with common BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer patients*	Prev-CO Prev- CA		Hospital for breast cancer cases General population	Breast cancer: incident Ashkenazi Jewish men and women referred for prenatal carrier testing	Inclusion: Controls: men and women undergoing prenatal screening Cases: Ashkenazi Jewish women who had surgery for breast cancer

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Eccles et al, 1998[141] *BRCA1 mutations in southern England*	England	Unselected	Case series	Prevalence	At least 2 relatives with breast cancer with average diagnosis age $\leq$ 40 years or at least 1 relative with breast cancer diagnosed < 45 years plus 1 relative with ovarian cancer diagnosed < 60 years.	230 Group 1: 155 Group 2: 45 Group 3: 30
FitzGerald et al, 1996[150] *Germ-line BRCA1 mutations in Jewish and non-Jewish women with early-onset breast cancer*	USA	Unselected	Case series	Prevalence	Not reported	418 30 diagnosed <30 39 Jewish
Fodor et al, 1998[125] *Frequency and carrier risk associated with common BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer patients*	USA	Ashkenazi Jewish	Case-control	Prevalence Actual risk: case-control data combined with population incidence rates Relative risk: comparison group was part of the study and population rates	High-risk: at least three 1st- or 2nd-degree relatives with breast cancer	268 breast cancer cases 1,715 prenatal screening group

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Eccles et al, 1998[141] *BRCA1 mutations in southern England*	Not reported	*BRCA1*	Screening with confirmation by sequencing: heteroduplex (HD) and SSCP analysis	Blood	Entire coding region	Not reported
FitzGerald et al, 1996[150] *Germ-line BRCA1 mutations in Jewish and non-Jewish women with early-onset breast cancer*	418 of 850 eligible women (49%)	*BRCA1*	Selected mutations: 185delAG--Jewish women Screening diagnosed <30: protein transcription translation (PTT) analysis	Blood	Entire coding region	418 women, of whom 39 were Jewish (9.3%)
Fodor et al, 1998[125] *Frequency and carrier risk associated with common BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer patients*	90% for breast cancer cases	*BRCA1* and *BRCA2*	Ashkenazi Jewish panel	Blood and tissue blocks from cases	N/A	<u>Prenatal Screening Group:</u> Mean age 35 <u>Breast Cancer Cases:</u> Mean age at diagnosis 58.7 (range 35-90)

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Eccles et al, 1998[141] *BRCA1 mutations in southern England*	18 protein-truncating mutations identified Group 1: 6.5% Group 2: None Group 3: 26.7%	Cancer was verified through family members, medical records, and death certificates when available. Only screening for mutation. Cannot evaluate the participation rate. Likely prevalent cases have bias.	Protein-truncating mutation
FitzGerald et al, 1996[150] *Germ-line BRCA1 mutations in Jewish and non-Jewish women with early-onset breast cancer*	Among 30 women with breast cancer diagnosed <30, 13% had definite, chain-termination mutations. Among 39 Jewish women with breast cancer diagnosed before ≤ 40, 21% had 185delAG mutation.	Cancer was verified. *BRCA1* only--good for diagnosis <30. Low participation rate--no information provided on comparability of participants and non-participants. Possible survivor bias.	Premature protein truncation, unambiguous inactivation of the gene product
Fodor et al, 1998[125] *Frequency and carrier risk associated with common BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer patients*	Carrier frequency: Breast cancer cases 7% Prenatal screening group 2% Lifetime risk of breast cancer for carriers 36%	Cancer was verified. Only did Ashkenazi Jewish panel. 90% participation rate for cases. No bias found.	Ashkenazi Jewish founder mutations

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Ford et al, 1998[131] *Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families*	Pen	BCLC	BCLC	Family history of breast and/or ovarian cancer	Inclusion: Family contained at least 4 cases of either female breast cancer diagnosed <60 years or male breast cancer diagnosed at any age
Frank et al, 1998[94] *Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family history and ovarian cancer risk*	Prev-CA		High-risk breast cancer clinic	Breast cancer: prevalent	Inclusion: 1. diagnosed with invasive breast cancer <50 years or ovarian cancer at any age 2. at least one 1st- or 2nd-degree relative with either breast or ovarian cancer Exclusion: 1. relative with a known mutation in *BRCA1* or *BRCA2* 2. family had been determined by linkage to carry a mutation in one of these genes

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Ford et al, 1998[131] *Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families*	USA, UK, Canada, Europe, Iceland	Unselected	Families	Actual risk: segregation analysis of family data	At least 4 cases of either female breast cancer diagnosed <60 years or male breast cancer diagnosed at any age	237 families
Frank et al, 1998[94] *Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family history and ovarian cancer risk*	USA	Unselected	Case series	Prevalence	At least one 1st- or 2nd-degree relative with either breast or ovarian cancer	238

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Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Ford et al, 1998[131] *Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families*	Not reported	*BRCA1* and *BRCA2*	Sequencing--subset Screening--various subset Flanking markers	Blood	N/A	Not reported
Frank et al, 1998[94] *Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family history and ovarian cancer risk*	Not reported	*BRCA1* and *BRCA2*	Sequencing	Blood	Entire coding region	84% had diagnosis of breast cancer <50 years, with no ovarian cancer 49% reported a history of ovarian cancer in themselves or at least one relative

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Ford et al, 1998[131] *Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families*	Cumulative breast cancer risk: by age 50, 28%; by age 70, 84% Cumulative ovarian cancer risk: by age 50, 0.4%; by age 70, 27% Possibly a lower breast cancer risk in *BRCA2* mutation carriers < 50 years old	Not all families genotyped at *BRCA1/BRCA2*. Estimated sensitivity 63%. No information on participation rate. Multiple case families--suitable for linkage analysis.	Linkage data: flanking markers for *BRCA1* and *BRCA2*, LoD scores *BRCA1* and *BRCA2* mutations not stated
Frank et al, 1998[94] *Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family history and ovarian cancer risk*	<u>Mutation frequency:</u> Overall: 39% With ovarian cancer in family: 50% Without ovarian cancer in family: 29%	Cancer was verified by probands. Good sequencing. No information participation rate. Prevalent cases bias.	Led to premature truncation of the *BRCA1* protein product at least 10 amino acids from the C-terminus or premature truncation of the *BRCA2* protein product at least 270 amino acids from the C-terminus

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Frank et al, 2002[33] *Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals*	Prev-CO		Clinical patient care	Breast cancer: prevalent Ovarian cancer: prevalent Family history of breast and/or ovarian cancer	Clinical testing
Gayther et al, 1999[149] *The contribution of germline BRCA1 and BRCA2 mutations to familial ovarian cancer: no evidence for other ovarian cancer-susceptibility genes*	Prev-CA	UKCCCR Study	National study of familial ovarian cancer	Ovarian cancer	<u>Inclusion:</u> Families containing 2 or more 1st- or 2nd-degree relatives with ovarian cancer

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Frank et al, 2002[33] *Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals*	USA	Unselected	Consecutive series tested	Prevalence	Not stated	10,000
Gayther et al, 1999[149] *The contribution of germline BRCA1 and BRCA2 mutations to familial ovarian cancer: no evidence for other ovarian cancer-susceptibility genes*	England	Unselected	Families	Prevalence	Two or more 1st- or 2nd-degree relatives diagnosed with epithelial ovarian cancer at any age	112 families

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Frank et al, 2002[33] *Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals*	Not relevant	*BRCA1* and *BRCA2*	Sequencing	Blood	Entire coding region	Age: median 49 (range 6-97) Gender: 90% women Race/ethnicity: 30% Ashkenazi Jewish 41% Northern/Western European
Gayther et al, 1999[149] *The contribution of germline BRCA1 and BRCA2 mutations to familial ovarian cancer: no evidence for other ovarian cancer-susceptibility genes*	Not reported	*BRCA1* and *BRCA2*	Screening with confirmation by sequencing: Protein truncation test and SSCA/HA Screening only: specific duplication (*BRCA1*)	Blood	Entire coding region	Not reported

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Frank et al, 2002[33] *Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals*	Mutation frequency: Women with breast cancer: 20% Women with ovarian cancer: 34%	Cancer was presumably verified for cases and family members. Sequencing good. Possible survivor bias.	Prematurely terminals the protein product of *BRCA1* at least 10 amino acids from the C-terminus or the protein product of *BRCA2* at least 110 amino acids from the C-terminus. Specific miss sense mutations and non-coding intervening sequence mutations--based on data derived from linkage analysis of high-risk families, functional assays, biochemical evidence, or demonstration of abnormal mRNA transcript processing. A few mutations: reservable presumption that the mutation was deleterious and reported as suspected deleterious.
Gayther et al, 1999[149] *The contribution of germline BRCA1 and BRCA2 mutations to familial ovarian cancer: no evidence for other ovarian cancer-susceptibility genes*	Mutation prevalence: 43% *BRCA1* prevalence: 36% *BRCA2* prevalence: 7% Extent of breast/ovarian cancer family history strongly predictive of *BRCA1* mutation status	Pathology report of death certificate verified for at least 2 ovarian cancer cases. Screening for coding regions good. Cannot evaluate participation rate or evidence of bias.	Predicted to result in premature truncation of *BRCA1* protein. Expected to affect splicing, predicted to abolish highly conserved splice-site consensus sequences. *BRCA1* Pro 1749Arg--functional studies suggest that it is functionally significant. *BRCA2* pathogenic mutations: frame shift deletion, nonsense mutation.

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Gershoni-Baruch et al, 2000[151] *Significantly lower rates of BRCA1/BRCA2 founder mutations in Ashkenazi women with sporadic compared with familial early onset breast cancer*	Prev-CA		Clinic	Breast cancer: prevalent	Inclusion: Diagnosed with breast cancer ≤ 42 years
Hartge et al, 1999[86] *The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews*	Prev-CO Prev- CA		General population	Breast and/or ovarian or other cancer: prevalent Responders to advertisement	Inclusion: Adult men and women
Hopper et al, 1999[132] *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*	Pen & Prev-CA	Australian Breast Cancer Family Study, Sydney	Cancer registry	Breast cancer: incident	Inclusion: Women under 40 years at time of diagnosis

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Gershoni-Baruch et al, 2000[151] *Significantly lower rates of BRCA1/BRCA2 founder mutations in Ashkenazi women with sporadic compared with familial early onset breast cancer*	Israel	Jewish	Case-series	Prevalence	1st or 2nd degree relative with breast/ovarian cancer	172
Hartge et al, 1999[86] *The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews*	USA	Jewish	Convenience sample	Prevalence	At least one 1st-degree relative with breast/ovarian cancer	5,318
Hopper et al, 1999[132] *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*	Australia	Unselected	Families	Actual risk: home-grown method applied to family data Segregation analysis of family data Relative risk: population rates	At least one 2nd degree relative affected with cancer	388 cases

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Gershoni-Baruch et al, 2000[151] *Significantly lower rates of BRCA1/BRCA2 founder mutations in Ashkenazi women with sporadic compared with familial early onset breast cancer*	Not reported	*BRCA1* and *BRCA2*	Ashkenazi Jewish panel	Blood	N/A	Mean age at cancer diagnosis: 37 (range 25-42) 46% had family history of breast/ovarian cancer 95% Ashkenazi Jewish
Hartge et al, 1999[86] *The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews*	Not relevant	*BRCA1* and *BRCA2*	Ashkenazi Jewish panel	Blood	N/A	Median age at diagnosis: 50 yrs 30% male 8% women with breast cancer 3% men with prostate cancer
Hopper et al, 1999[132] *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*	Interviewed 73% Blood drawn in 90% with affected 1st degree relative Blood drawn in 82% without affected 1st degree relative Blood drawn on 60% of total group	*BRCA1* and *BRCA2*	Screening with confirmation by sequencing: MHA, protein truncation test	Blood	Exon 2, 11 & 20 *BRCA1* Exon 10 & 11 *BRCA2*	Not reported

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Gershoni-Baruch et al, 2000[151] *Significantly lower rates of BRCA1/BRCA2 founder mutations in Ashkenazi women with sporadic compared with familial early onset breast cancer*	Mutation frequency: Overall: 31% Family history of breast and/or ovarian cancer: 57% No such family history: 10%	Cancer was verified. Ashkenazi Jewish panel only. No information on participation rate. Possible survivor bias.	Ashkenazi Jewish founder mutations
Hartge et al, 1999[86] *The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews*	Most important predictor of having a mutation is previous diagnosis of breast and/or ovarian cancer. For men and women without cancer, family history of breast cancer diagnosed <50 years was strongest predictor.	Cancer was not verified. Ashkenazi Jewish panel only. Ad responders. Cancer cases--possible survivor bias. General--volunteer; possibly more likely to have a positive family history.	Ashkenazi Jewish founder mutations
Hopper et al, 1999[132] *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*	Family history of breast cancer was not a strong predictor of mutation status in this setting. Risk in mutation carriers was, on average, 9 times the population risk (95% CI 4-23). Penetrance to age 70 was 40% (95% CI 15-65%), about half that estimated from BCLC families.	Cancer verified in cases--excellent Family members--very good (verification of reported cancer sought through records) Mutation identification was fair (2/3 coding region). Participation rate was fair, no differences in measured risk factors.	Protein-truncating mutation

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Janezic et al, 1999[148] *Germline BRCA1 alterations in a population-based series of ovarian cancer cases*	Prev-CA		Cancer registry	Ovarian cancer: incident	Inclusion: Diagnosed between 3/94-2/95
King et al, 2003[134] *Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2*	Pen & Prev-CA		Cancer center	Breast cancer: incident	Inclusion: Diagnosed between 9/96-12/00

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Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Janezic et al, 1999[148] *Germline BRCA1 alterations in a population-based series of ovarian cancer cases*	USA	Unselected	Case series	Prevalence	At least one 1st-degree relative with breast cancer diagnosed before 50 years or ovarian cancer	107
King et al, 2003[134] *Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2*	USA	Ashkenazi Jewish	Retrospective Cohort	Actual risk: survival analysis for relatives who have a confirmed *BRCA1/BRCA2* mutation	Ashkenazi Jewish	1,008 probands 104 families Number of *BRCA1/2* mutation positive family members not stated

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Janezic et al, 1999[148] *Germline BRCA1 alterations in a population-based series of ovarian cancer cases*	82%	*BRCA1*	Screening with confirmation by sequencing: RNase mismatch cleavage assay	Blood	Entire coding region	Mean age at cancer diagnosed: 55.04 100% women
King et al, 2003[134] *Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2*	Not reported	*BRCA1* and *BRCA2*	Ashkenazi Jewish panel	Blood Archived tissue--deceased family members	N/A	Age at diagnosis 10% <40 13% 40-44 19% 45-49 30% 50-59 27% 60+

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Author, year	Conclusions	Study quality	Definition of clinically significant
Janezic et al, 1999[148] *Germline BRCA1 alterations in a population-based series of ovarian cancer cases*	Several variants (novel and characterized) and a rare form of the Q356R polymorphism were associated with a family history of cancer, suggesting that these may influence ovarian cancer risk.	Cancer was verified. *BRCA1* only--good identification, screening. Good participation rate--82%; no analysis of possible bias.	Protein-truncating mutation
King et al, 2003[134] *Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2*	Lifetime risk of breast cancer among women mutation carriers is 82%, similar to risk in families with many cases.	Cancer was verified through probands, presumably. Relatives confirmed by pathology report or death certificate. Ashkenazi Jewish panel only. No info on participation rate. No evidence of bias.	Ashkenazi Jewish founder mutations

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Langston et al, 1996[142] *BRCA1 mutations in a population-based sample of young women with breast cancer*	Prev-CA	Daling et al, 1994[244]	Cancer registry	Breast cancer: prevalent	Inclusion: 1. early onset breast cancer diagnosed before age 35 2. Caucasian 3. not selected on basis of family history 4. born after 1944 5. diagnosed between 1/1/1983 and 4/30/1990 6. residents of King, Pierce, or Snohomish County in Washington state 7. women 8. identified through the Cancer Surveillance System

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Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Langston et al, 1996[142] *BRCA1 mutations in a population-based sample of young women with breast cancer*	USA	Caucasian	Population-based, case-control	Prevalence	At least one 1st-degree relative with breast/ovarian cancer. At least one 2nd-degree relative (no 1st-degree) with breast/ovarian cancer	80

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Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Langston et al, 1996[142] *BRCA1 mutations in a population-based sample of young women with breast cancer*	84% interviewed 52% of those interviewed gave blood sample 37% of overall were age eligible	*BRCA1*	Screening with confirmation by sequencing: SSCPs. Allele-specific oligonucleotides	Blood	Entire coding region, intron-exon boundaries promoter region	100% Caucasian women. Age at diagnosis for all women with breast cancer before age 35 (n=214): 21-30 age range = 70 (33%) 31-34 age range = 143 (67%) Age at diagnosis for women tested for *BRCA1* before age 35 (n=80): 21-30 age range = 26 (32%) 31-34 age range = 54 (68%)

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Langston et al, 1996[142] *BRCA1 mutations in a population-based sample of young women with breast cancer*	Alterations in *BRCA1* identified in ~10% of young women with breast cancer, and were not limited to those with a positive family history of breast/ovarian cancer.	Cancer was verified. Completeness of mutation was okay--screening. Low participation rate. Participants: 94% alive; 19% in situ. Non-participants: 66% alive; 69% in situ. Survivors less extensive breast cancer.	Associated with breast cancer in previous studies of high-risk families or predicted to result in protein truncation.

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Liede et al, 2002[129] *Cancer incidence in a population of Jewish women at risk of ovarian cancer*	Pen & Prev-CA	Gilda Radner Ovarian Cancer Detection Program	Ovarian cancer screening program based in a major medical center	Healthy women with a family history of breast cancer or ovarian cancer	Inclusion: 1. Jewish (self-report) 2. attended more than one appointment and observed for at least a year 3. family history of ovarian cancer (any age) or breast cancer (younger than 50 years) in a 1st or 2nd degree relative 4. aged 35 or older
Malone et al, 2000[143] *Frequency of BRCA1/BRCA2 mutations in a population-based sample of young breast carcinoma cases*	Prev-CO Prev- CA	Combines data from two case-control studies: Daling et al, 1994[244] and Brinton et al, 1995[245]	Cancer registry	Breast cancer: incident and Prevalent	Inclusion: 1. incident cases of early-onset breast cancer diagnosed before age 45 2. any race 3. diagnosed between 1/1/1983 and 12/31/1992 4. residents of King, Pierce, or Snohomish County in Washington state 5. women 6. identified through the Cancer Surveillance System 7. not selected on basis of family history

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Liede et al, 2002[129] *Cancer incidence in a population of Jewish women at risk of ovarian cancer*	USA	Jewish	Cohort	Actual risk: method for calculating risk: survival analysis	1st or 2nd degree relative with a family history of ovarian cancer (any age) or breast cancer (before age 50)	290
Malone et al, 2000[143] *Frequency of BRCA1/BRCA2 mutations in a population-based sample of young breast carcinoma cases*	USA	Unselected	Population-based, case-control	Prevalence	Diagnosed before 35 or 45 (two different studies used) Diagnosed $\leq$ 45 and 1st-degree relative with breast cancer	2,085 cases; 1,736 controls

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Liede et al, 2002[129] *Cancer incidence in a population of Jewish women at risk of ovarian cancer*	475 eligible, 83 excluded because they had < 1 year follow-up; 290 in analysis. DNA specimens for 213 (73.4%)	*BRCA1* and *BRCA2*	Selected mutations: Ashkenazi Jewish panel Sequencing of coding regions for women with incident breast or ovarian cancer who did not have a Jewish founder mutation	Blood	Entire coding region, if sequenced	Age: mean: 44.8; 40.4 for mutation carriers Gender: 100% women Race/ethnicity: Jewish (self-report)
Malone et al, 2000[143] *Frequency of BRCA1/BRCA2 mutations in a population-based sample of young breast carcinoma cases*	1st data set: Not clear, but same study used by Langston et al, 1996. Blood collected from 592 cases and 165 controls 2nd data set: 648 cases interviewed; blood collected from 545 (84%); 610 controls interviewed; blood taken from 473 (77.5%)	*BRCA1* and *BRCA2*	Screening with confirmation by sequencing: SSCP	Blood	Entire coding region, intron-exon boundaries promoter region	100% women 96.6% Caucasian, 1% African American, 1.6% Asian/Pacific Islander, 0.3% American Indian/Aleutian, 0.6% "Other"

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Liede et al, 2002[129] *Cancer incidence in a population of Jewish women at risk of ovarian cancer*	Excess risk of breast and ovarian cancer in Jewish women with a family history of ovarian cancer is largely due to mutations in *BRCA1*. Intensive surveillance with CA-125 and ultrasound does not seem to be an effective means of diagnosing early stage ovarian cancer in this high-risk cohort.	Cancer verified by medical and pathology review Only addresses Jewish founder mutations; small chance that non-carriers had a mutation Tested: younger, more likely to have ovarian cancer family history, longer follow-up: 7.2 ± 1.7, compared with 5.3 ± 2.2 overall Not tested: more missing family history	Ashkenazi Jewish founder mutations
Malone et al, 2000[143] *Frequency of BRCA1/BRCA2 mutations in a population-based sample of young breast carcinoma cases*	Mutation frequency: Diagnosed <35, unselected for family history: 9.4% Diagnosed <45, with breast cancer in 1st-degree relative: 12% NOTE: These groups overlap.	Cancer was verified. Completeness of mutation is okay, screening. Low participation rate. Survivors less extensive breast cancer.	Frame shift mutations result in premature stop colons, most noted in other high-risk families and listed in BIC.

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Modan et al, 2001[127] *Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation*	Prev-CO		General population	Ovarian cancer: incident	Inclusion: Women pathologically confirmed ovarian cancer or primary peritoneal carcinoma, possibly of ovarian origin
Moslehi et al, 2000[135] *BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer*	Pen & Prev-CA		Hospital	Ovarian cancer; prevalent cases	Inclusion: Cases: Jewish women with ovarian cancer in 11 hospitals, and subjects identified through the Ontario Cancer Registry as part of genetics study. Controls: Jewish women with no history of breast or ovarian cancer recruited from staff of 7 participating hospitals or invited from membership lists of a synagogue and Jewish women's group.

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Modan et al, 2001[127] *Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation*	Israel	Jewish	Case-control	Prevalence	Intermediate risk: one 1st-degree relative with breast cancer High risk: one 1st-degree relative with ovarian cancer or at least two 1st-degree relatives with breast cancer	840 cases 751 controls
Moslehi et al, 2000[135] *BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer*	North America and Israel	Jewish	Case-control	Prevalence Actual risk: Kin-cohort method Relative Risk: comparison group was part of the study	Familial: 1 case of familial ovarian cancer (other than proband) or 2 cases of early-onset breast cancer (< age 50 at diagnosis) in 1st and 2nd degree relatives of proband	213 Jewish women with ovarian cancer 386 Ashkenazi Jewish women without ovarian or breast cancer

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Modan et al, 2001[127] *Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation*	85% of peritoneal or epithelial ovarian cancer interviewed 75% of those interviewed had genetic test results 67% of controls were interviewed 78% of controls interviewed had genetic test results	*BRCA1* and *BRCA2*	Ashkenazi Jewish panel	Blood Buccal cells, tumor specimens	N/A	Cases: 3.7% <40 years 19.4% 40-49 24.4% 50-59 29% 60-69 23.5% ≥ 70 years 71.5% Ashkenazi Jewish 23% Not Ashkenazi Jewish 5.5% mixed Controls: matched for age (+/- 2 years)
Moslehi et al, 2000[135] *BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer*	465 potential case subjects. 80 dead, 98 not able to locate. 33 excluded due to diagnosis other than invasive epithelial ovarian cancer. 254 invited to participate, 213 completed family history questionnaire and 208 provided blood sample (208/254 = 82%). 49 refused to participate.	*BRCA1* and *BRCA2*	Ashkenazi Jewish panel	Blood	N/A	Case: women with ovarian cancer. Mean age at time of interview: 61.2 years (21 - 90).

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Modan et al, 2001[127] *Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation*	Mutation frequency: Cases: 29% Controls: 1.7%	Cancer was verified pathologically. Ashkenazi Jewish panel was complete. 5% of cases died before interview; 4% were too sick. Modest bias for cases: no difference in age or ancestry for tested versus not tested. Those tested were slightly more likely to have breast/ovarian cancer in their family history.	Ashkenazi Jewish founder mutations
Moslehi et al, 2000[135] *BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer*	Founder mutation frequency: Cases: 41% Cumulative ovarian cancer risk to age 75: 1st-degree relatives of cases: 6.3% 1st-degree relatives of controls: 2.0%	Cancer verified through probands, presumably. Good completeness of mutations--most mutations are founder mutations in this paper. Low participation rate. Survivor bias.	Ashkenazi Jewish founder mutations

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Newman et al, 1998[145] *Frequency of breast cancer attributable BRCA1 in a population-based series of American women*	Prev-CA	Women in Carolina Breast Cancer Study	Conducted at home	Breast cancer: incident No cancer	Inclusion: Women aged 20-74 at diagnosis
Oddoux et al, 1996[128] *The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%*	Prev-CO Prev- CA		Heterozygote detection from autosomol recessive conditions	Breast cancer: prevalent General reproductive population	Inclusion: Men and women
Peto et al, 1999[29] *Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer*	Prev-CA	U.K. National Case Control Study Group	Cancer Registry	Breast cancer: prevalent	Inclusion: 1. women diagnosed before age 36 years or 2. women diagnosed between 36 and 45 years

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Newman et al, 1998[145] *Frequency of breast cancer attributable BRCA1 in a population-based series of American women*	USA	Unselected	Case-control	Prevalence	High risk- 4 or more affected family members, including the proband	211 cases 188 controls
Oddoux et al, 1996[128] *The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%*	USA	Ashkenazi and non-Jewish individuals	Convenience sample	Prevalence	Breast or ovarian cancer in a first or second degree relative--for breast cancer cases only (Memorial Sloan-Kettering Cancer Center)	1,255 Ashkenazi Jewish 519 non-Ashkenazi Jewish Cases: 107 with breast/ovarian cancer family history
Peto et al, 1999[29] *Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer*	England	Unselected	Case-control	Prevalence	A mother or sister affected with breast cancer before the age of 60 years	617

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Newman et al, 1998[145] *Frequency of breast cancer attributable BRCA1 in a population-based series of American women*	77% cases interviewed 68% controls interviewed Blood sample taken from 95% of interviewed	*BRCA1*	Selected mutations: 8 specific mutations Screening with confirmation by sequencing: protein truncation test--exon 11, multiplex SSCA	Blood	Entire coding region Splice junctions and neighboring intronic regions 5' and 3' untranslated regions	56% Caucasian 41% African American 36% between 40-49 years 27% between 60-74 years
Oddoux et al, 1996[128] *The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%*	Not reported	*BRCA2*	Selected mutations: *BRCA2* 6174delT	Blood	N/A	Not reported
Peto et al, 1999[29] *Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer*	1,399 original sample 44% analyzed	*BRCA1* and *BRCA2*	Screening with confirmation by sequencing: CSGE	Blood	Entire coding region Splice-site junctions	41% diagnosed <36 59% diagnosed 36-45

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Newman et al, 1998[145] *Frequency of breast cancer attributable BRCA1 in a population-based series of American women*	Estimated mutation frequencies: 3.3% white women with breast cancer 0% black women with breast cancer 23% white women with breast cancer and family history of ovarian cancer 13% white women with breast cancer and high risk, but no ovarian cancer 33% white women with breast cancer and family history of breast/ovarian cancer	Cancer was verified. Completeness of mutation is okay, screening and common European mutations. Moderate participation rate--no comparison of participants and non-participants. No evidence of bias.	Protein truncating [Intron 5 splicing mutation--leads to aberrant mRNA, seen in other high-risk families; nonsense mutation--causes immediate stop in translation at codon 780]
Oddoux et al, 1996[128] *The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%*	Findings suggest a difference in cumulative lifetime prevalence for *BRCA1* and *BRCA2* in Ashkenazi persons. Genetic counseling should be tailored to reflect different risks of the two mutations.	Verification of cancer was not reported. Complete identification of Ashkenazi Jewish *BRCA2* founder mutation. Participation rate was not reported. Possible survivor bias for cases, no information available for controls.	Ashkenazi Jewish founder mutations
Peto et al, 1999[29] *Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer*	Mutations in *BRCA1* and *BRCA2* genes make equal contributions to early-onset breast cancer, and account for a small proportion of familial breast cancer risk.	Cancer was verified. Sensitivity of test estimated at 63%. Low participation rate. Possible survivor bias.	Predicted to encode truncated proteins

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Risch et al, 2001[133] *Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer*	Pen & Prev-CA		Cancer registry	Ovarian cancer: incident	Inclusion: 1. women 2. aged 20-79 at diagnosis 3. Ontario resident at diagnosis
Roa et al, 1996[12] *Ashkenazi Jewish population frequencies fro common mutations in BRCA1 and BRCA2*	Prev-Co		Screening population for conditions common among Ashkenazi Jews	Reproductive age population	Inclusion: Women and men
Robson et al, 1998[153] *BRCA-associated breast cancer in young women*	Prev-CA	Offit, 1996[247]; Neuhausen et al, 1996[13]; Oddoux et al, 1996[127]	Cancer center	Breast cancer: prevalent	Inclusion: 1. diagnosed with breast cancer before age 42 2. participated in studies at Memorial Sloan-Kettering Cancer Center between January 1992 and December 1995 3. Jewish ancestry

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Risch et al, 2001[133] *Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer*	Canada	Unselected	Case series	Prevalence Actual risk: method for calculating risk: kin-cohort method (Wacholder et al, 1998[246]) Relative risk: comparison group for relative risk: part of the study	Risk level: potential familiarity Definition: 1st degree ovarian or breast cancer and < 60 years old **OR** 2 1st- or 2nd-degree relatives with breast or ovarian cancer	649 people
Roa et al, 1996[12] *Ashkenazi Jewish population frequencies fro common mutations in BRCA1 and BRCA2*	Israel	Ashkenazi Jewish	Convenience sample	Prevalence Relative risk: comparison group was based on attributable risk and mutation frequency estimator	None	3,116
Robson et al, 1998[153] *BRCA-associated breast cancer in young women*	USA	Jewish	Case series	Prevalence	Breast or ovarian cancer in at least 1 1st- or 2nd-degree relative	91

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Risch et al, 2001[133] *Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer*	Group description: tested Participation rate: 63% total group 375 non-participants: 197 deaths, 76 refused, 57 too ill, 5 MD refused, 8 lost	*BRCA1* and *BRCA2*	Combination of methods: Selected mutations Ashkenazi Jewish panel and other with 11 mutations total Screening with confirmation by sequencing protein truncation test (PTT) and DGGE (fluorescent multiplex denaturing gradient gel electrophoresis)	N/A	Entire coding region Intron-exon boundaries	Not reported
Roa et al, 1996[12] *Ashkenazi Jewish population frequencies fro common mutations in BRCA1 and BRCA2*	Not reported	*BRCA1* and *BRCA2*	Selected mutations: Ashkenazi Jewish panel C61G, 4184 del TCAA (*BRCA1*)	Blood	N/A	Not reported
Robson et al, 1998[153] *BRCA-associated breast cancer in young women*	91 tested Complete *BRCA1* testing in 64 cases; 4 underwent targeted sequencing testing; 7 withdrew from study; 12 lost to attrition; 79 completed testing for *BRCA2*	*BRCA1* and *BRCA2*	Sequencing and Ashkenazi Jewish panel	Blood	Entire coding region and intron-exon boundaries for those sequenced	100% Jewish women. Median age at diagnosis = 36 years (range 21-42)

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Risch et al, 2001[133] *Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer*	No mutations found in women with tumors of borderline histology. Mutation frequency among women with invasive cancers was 12% *BRCA1* mutation carriers: penetrance by age 80=36% for ovarian cancer and 68% for breast cancer. For *BRCA2* mutations, excess of breast cancer was observed only for mutations outside of the ovarian cancer-cluster region (OCCR).	Participation rate: 63% Evidence of bias: Survivor bias? 19% eligible cases deceased Family history not confirmed	All identified mutations deleterious, founder mutations, PTT--mutations associated with shortened, nonfunctional proteins, DGGE--all previously seen, and known to be deleterious (BIC database)
Roa et al, 1996[12] *Ashkenazi Jewish population frequencies fro common mutations in BRCA1 and BRCA2*	*BRCA1* 185 del Ag (1.1%) and *BRCA2* 6174 del T (1.5%) mutations are the second most common mutations predisposing to breast cancer among Ashkenazi Jews.	Ashkenazi Jewish panel good, participation rate not reported. Possible bias with reproductive age population.	Ashkenazi Jewish founder mutations
Robson et al, 1998[153] *BRCA-associated breast cancer in young women*	<u>Mutation frequency:</u> Overall: 33%	Cancer was verified. Ashkenazi panel and sequencing--good. Original participation rate not reported. Possible survivor bias	Ashkenazi Jewish founder mutations. Premature truncation of the protein product (*BRCA2* 9325insA)

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Satagopan et al, 2001[137] *The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations*	Pen & Prev-CO Prev-CA	Control population obtained via Struewing et al. 1997[11]	3 hospitals and a large series of unaffected survey participants	Breast cancer - incident and a large series of unaffected participants	Inclusion: women Cases: 2. clinical records of all incident cases of breast cancer between 1980-1995. 3. women who self-identified as Jewish 4. received breast-conserving therapy 5. diagnosed on or before age 65 Controls: 1. self-identified as Jewish 2. no previous breast or ovarian cancer
Satagopan et al, 2002[136] *Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations*	Pen		Hospital General population	Ovarian cancer: incident (series 1) and prevalent (series 2) Controls had no cancer.	Inclusion: Women Exclusion: Personal history of breast cancer

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Satagopan et al, 2001[137] *The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations*	USA & Canada	Self-identified as Jewish	Case-control	Prevalence Actual risk: case-control data combined with population incidence rates Relative risk: comparison group was part of the study	Cases were unselected for family history of breast cancer	782 cases 3,434 controls
Satagopan et al, 2002[136] *Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations*	USA & Israel	Ashkenazi Jewish--series 1 Jewish--series 2 and controls	Case-control	Prevalence Actual risk: case-control data combined with population incidence rates Relative risk: comparison group was part of the study	Not reported	382 cases 3,434 controls

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Satagopan et al, 2001[137] *The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations*	Cases: 900 met inclusion criteria. 782 were analyzed (87%). Controls: 3,434 At the three centers participation was as follows: 78% Memorial Sloan-Kettering Cancer Center 100% Sir Mortimer B. Davis Jewish General Hospital 90% Mount Sinai Medical Center	*BRCA 1* and *BRCA2*	Selected mutations: Ashkenazi Jewish panel	Stored tissue samples and archival tissues	N/A	Age at diagnosis Cases: 64% age 50 +, 26% age 40-49, 9% < age 40. Controls: 47% age 50+, 26% age 40-49; 20% < 40 years
Satagopan et al, 2002[136] *Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations*	Not reported	*BRCA1* and *BRCA2*	Ashkenazi Jewish panel	Blood Archival tissue	N/A	100% women

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Satagopan et al, 2001[137] *The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations*	*BRCA1:* Relative risk of breast cancer estimated 21.6 in women < 40, 9.6 in those aged 40-49, and 7.6 in women ≥ 50. Penetrance of breast cancer at age 70 among *BRCA1* mutation carriers: 46% (95% confidence, 31-80%) rising to 59% (95% confidence, 40-93%) at age 80. *BRCA2:* Relative risks in same three age categories estimated to be 3.3, 3.3, and 4.6, respectively, with a penetrance at age 70 of 26% (95% confidence, 14-50%), rising to 38% (95% confidence, 20-68%) at age 80. Lifetime risk of breast cancer in Jewish women who are mutation carriers estimated with this approach is substantially lower than reported estimates using multiple-case families. Risks appear to be different for carriers of *BRCA1* and *BRCA2* mutations.	Control selection: Volunteers from public advertisements, not population-based; different geographic area than cases Case selection: Hospital-based	Ashkenazi Jewish founder mutations
Satagopan et al, 2002[136] *Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations*	Lifetime penetrance: *BRCA1:* lower than estimates obtained using family data of multiple affected members, but larger than estimates from some population-based proband series *BRCA2:* in the range reported by some family studies	Control selection: Volunteers from public advertisements, not population based; different geographic area than cases Case selection: Hospital based	Ashkenazi Jewish founder mutations

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Stratton et al, 1997[147] *Contribution of BRCA1 mutations to ovarian cancer*	Prev-CA		Hospital	Ovarian cancer: incident, prevalent	Inclusion: 1. women 2. diagnosed < 70 years of age Exclusion: 1. men 2. ≥ age 70 at diagnosis
Struewing et al, 1995[126] *The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals*	Prev-CO		General population Genetic screening for cystic fibrosis and Tay-Sachs	Reproductive age, unselected for personal or family cancer history	Inclusion: Women and men
Struewing et al, 1997[11] *The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews*	Pen & Prev-CO Prev-CA		General population convenience sample	Convenience sample	Inclusion: > 20 years of age

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Stratton et al, 1997[147] *Contribution of BRCA1 mutations to ovarian cancer*	London, England	Unselected	Case series	Prevalence	N/A	386 people; 374 = DNA amplification OK
Struewing et al, 1995[126] *The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals*	USA & Israel	Ashkenazi Jewish	Convenience sample	Prevalence	N/A	858
Struewing et al, 1997[11] *The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews*	USA	Jewish	Families	Prevalence	1st-degree relative with breast/ovarian cancer	5,331 individuals

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Stratton et al, 1997[147] *Contribution of BRCA1 mutations to ovarian cancer*	Group description: ovarian cancer cases Participation rate: 80% contacted, 80% total group	*BRCA1*	Screening with confirmation by sequencing: MHA	Blood	Entire coding region Intron-exon boundaries	Age: mean or median NS, range NS Diagnosis and ages: <40 10%, 40-49 22%, 50-59 41%, 60-69 27%. Gender: 100% women Race/ethnicity: NS
Struewing et al, 1995[126] *The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals*	Not reported	*BRCA 1*	Selected mutations: Ashkenazi Jewish panel	Blood	N/A	Not reported
Struewing et al, 1997[11] *The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews*	7 excluded because of adoption 6 excluded for other reasons	*BRCA1* and *BRCA2*	Ashkenazi Jewish panel	Blood	N/A	Age: mean NS 29% 40-49, 24% 50-59 Gender: 70% women Race/ethnicity: 100% Ashkenazi Jewish

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Stratton et al, 1997[147] *Contribution of BRCA1 mutations to ovarian cancer*	Assuming lab test sensitivity of 70%, *BRCA1* mutations occur in 5% (95% CI: 3-18%) of women diagnosed with ovarian cancer before age 70.	Cancer verified: yes, histopathology Completeness of mutation identification: est. 70% sensitivity Participation rate: very good 80% Evidence of bias: yes, includes incident and prevalent cases	Predicted to result in a truncated protein. Novel variant (314 del GAT), resulted in frame detection adjacent to the ring-finger domain--occurred at residue conserved in both mice and humans
Struewing et al, 1995[126] *The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals*	1 in 100 women of Ashkenazi Jewish descent may be at especially high risk of developing breast/ovarian cancer.	*BRCA1* only 185 del AG, subset only for 5382 ins C. Participation rate not reported.	Ashkenazi Jewish founder mutations
Struewing et al, 1997[11] *The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews*	Over 2% of Ashkenazi Jews have a *BRCA1* or *BRCA2* mutation that increases breast and ovarian cancer risk. Risk of breast cancer among this population of mutation carriers is 33% by age 50 and 56% by age 70. These are lower than prior estimates. Risk of ovarian cancer among the same group was 16% by age 70.	Ashkenazi Jewish panel good, Convenience sample: higher risk individuals may have volunteered.	Ashkenazi Jewish founder mutations

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Sutcliffe et al, 2000[146] *Ovarian and breast cancer risks to women in families with two or more cases of ovarian cancer*	Prev-Ca	UKCCCR Familial Ovarian Cancer Registry	Cancer registry	Families with at least two 1st-degree relatives with ovarian cancer	Inclusion: 1. 1st-degree female relatives of family members who have ovarian cancer or breast cancer before age 50; all breast/ovarian cancer cases 2. participated in UKCCCR Familial Ovarian Cancer Registry 3. registered in January 1991 or later

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Sutcliffe et al, 2000[146] *Ovarian and breast cancer risks to women in families with two or more cases of ovarian cancer*	UK	Women from England and Wales	Families	Prevalence	Risk determined by number of 1st- or 2nd-degree relatives with breast or ovarian cancer.	112 families

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Sutcliffe et al, 2000[146] *Ovarian and breast cancer risks to women in families with two or more cases of ovarian cancer*	N/A	*BRCA1* and *BRCA2*	Screening with confirmation by sequencing: protein truncation test and SSCA/HA Screening only: specific duplication (*BRCA1*)	Blood	Entire coding region	100% women Relative risks given, but not demographics for age

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Sutcliffe et al, 2000[146] *Ovarian and breast cancer risks to women in families with two or more cases of ovarian cancer*	Mutation frequency: Ovarian cancer: 49% Breast cancer: 49%	Cancer confirmed by histology, death certificate, cancer registry, medical records. Screening for coding regions good. Participation rate can't be evaluated. Bias can't be evaluated.	Predicted to result in premature truncation of *BRCA1* protein. Expected to affect splicing, predicted to abolish highly conserved splice-site consensus sequences. *BRCA1* Pro 1749Arg--functional studies suggest that it's functionally significant. *BRCA2* pathogenic mutations: frame shift deletion, nonsense mutation.

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Data type	Data source / Parent study	Setting	Population	Inclusion / Exclusion criteria
Warner et al, 1999[138] *Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer*	Prev-CA		Oncology centers in Toronto and Montreal	Breast cancer: prevalent No cancer	Case Inclusion: 1. living 2. Jewish 3. women 4. unselected age 5. diagnosed with invasive breast cancer before 5/1/1998 6. followed at 1 of 6 oncology centers in Toronto or Montreal Cases Exclusion: 1. Sephardic 2. converted to Judaism 3. adopted Control Patients Inclusion: 1. non-Jewish women 2. with breast cancer Control Subjects Inclusion: 1. Jewish women 2. aged 25-88 3. without breast cancer Control Exclusion: 1. history of breast or ovarian cancer 2. Sephardic 3. converted to Judaism 4. adopted

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Country	Race or ethnicity	Study design	Primary risk measure	Family history / Risk level definition	N
Warner et al, 1999[138] *Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer*	Canada & USA	Ashkenazi Jewish for cases and controls Non-Jewish with breast cancer	Case-control Families	Prevalence Actual risk: Kin-cohort method	1st-, 2nd-, or 3rd-degree relatives with breast or ovarian cancer	412 Jewish breast cancer cases 48 1st-degree relatives of mutation positive cases

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied	Demographics
Warner et al, 1999[138] *Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer*	700 contacted and 457 (65.3%) agreed to participate; 412 (90%) had genetic testing 360 non-Jewish controls with breast cancer; and 380 Jewish control without breast cancer	*BRCA1* and *BRCA2*	Ashkenazi Jewish panel	Blood	N/A	Age: mean 61.1 for cases; 59.1 for non-Jewish controls; 52.6 for Jewish controls Mean age at diagnosis: 54.3 for Jewish breast cancer cases; 53.2 for non-Jewish breast cancer cases. Gender: 100% women

Appendix I. Evidence Table of Studies of Prevalence and Penetrance

Author, year	Conclusions	Study quality	Definition of clinically significant
Warner et al, 1999[138] *Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer*	Mutation prevalence: 11.7% Estimated penetrance to age 70 for breast cancer: *BRCA1* gene mutations: 59.9% *BRCA2* gene mutations: 28.3%	Cancer was verified through pathology records for cases. Ashkenazi Jewish panel only. Modest participation rate, participants and non-participants were not compared. Possible survivor bias.	Ashkenazi Jewish founder mutations

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Abeliovich et al, 1997[152]	Hospital-based (Israel) AJ women	B	Y	FH-NS	185	19	10	29	10.3%	5.4%	15.7%
Abeliovich et al, 1997	Hospital-based (Israel) AJ women	B	Y	Hgh	64	16	5	21	25.0%	7.8%	32.8%
Abeliovich et al, 1997	Hospital-based (Israel) AJ women	B	Y	Mod	99	3	7	10	3.0%	7.1%	10.1%
Abeliovich et al, 1997	Hospital-based (Israel) AJ, age: < 30 yrs	B	Y	FH-NS	6	1	2	3	16.7%	33.3%	50.0%
Abeliovich et al, 1997	Hospital-based (Israel) AJ, age: 30-40 yrs	B	Y	FH-NS	38	10	1	11	26.3%	2.6%	28.9%
Abeliovich et al, 1997	Hospital-based (Israel) AJ, age: 40-50 yrs	B	Y	FH-NS	65	3	3	6	4.6%	4.6%	9.2%
Abeliovich et al, 1997	Hospital-based (Israel) AJ, age: 50-65 yrs	B	Y	FH-NS	59	4	4	8	6.8%	6.8%	13.6%
Abeliovich et al, 1997	Hospital-based (Israel) AJ, age: > 65 yrs	B	Y	FH-NS	17	1	0	1	5.9%	0.0%	5.9%
Abeliovich et al, 1997	Hospital-based (Israel) AJ women	O	Y	FH-NS	21	7	6	13	33.3%	28.6%	61.9%
Abeliovich et al, 1997	Hospital-based (Israel) AJ, age: < 30 yrs	O	Y	FH-NS	0	0	0	0	.	.	.
Abeliovich et al, 1997	Hospital-based (Israel) AJ, age: 30-40 yrs	O	Y	FH-NS	1	1	0	1	100.0%	0.0%	100.0%
Abeliovich et al, 1997	Hospital-based (Israel) AJ, age: 40-50 yrs	O	Y	FH-NS	5	1	1	2	20.0%	20.0%	40.0%
Abeliovich et al, 1997	Hospital-based (Israel) AJ, age: 50-65 yrs	O	Y	FH-NS	12	4	4	8	33.3%	33.3%	66.7%

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Abeliovich et al, 1997	Hospital-based (Israel) AJ, age: > 65 yrs	O	Y	FH-NS	3	1	1	2	33.3%	33.3%	66.7%
Anglian Breast Cancer Study Group, 2000[27]	Population-based series (UK), diagnosed < 55 yrs	B	N	FH-NS	1,435	8	16	24	0.6%	1.1%	1.7%
Anglian Breast Cancer Study Group, 2000	Population-based series (UK), diagnosed < 55 yrs	B	N	Avg	1,124	.	.	11	.	.	1.0%
Anglian Breast Cancer Study Group, 2000	Population-based series (UK), diagnosed < 55 yrs	B	N	Mod	197	.	.	7	.	.	3.6%
Anglian Breast Cancer Study Group, 2000	Population-based series (UK), diagnosed < 55 yrs	B	N	Hgh	27	.	.	4	.	.	14.8%
Anglian Breast Cancer Study Group, 2000	Population-based series (UK), diagnosed < 55 yrs Age: < 35	B	N	FH-NS	57	2	4	6	3.5%	7.0%	10.5%
Anglian Breast Cancer Study Group, 2000	Population-based series (UK), diagnosed < 55 yrs Age: 35-44	B	N	FH-NS	341	3	4	7	0.9%	1.2%	2.1%
Anglian Breast Cancer Study Group, 2000	Population-based series (UK), diagnosed < 55 yrs Age: 45-54	B	N	FH-NS	917	3	8	11	0.3%	0.9%	1.2%
Anton-Culver et al, 2000[144]	Population-based (US)	B	N	FH-NS	671	11	.	.	1.6%	.	.
Anton-Culver et al, 2000	Population-based (US)	B	N	Avg	432	5	.	.	1.2%	.	.
Anton-Culver et al, 2000	Population-based (US)	B	N	Mod	120	4	.	.	3.3%	.	.
Anton-Culver et al, 2000	Population-based (US)	B	N	Hgh	29	2	.	.	6.9%	.	.
Anton-Culver et al, 2000	AJ (US) Breast cancer	B	Y	FH-NS	30	2	.	.	6.7%	.	.
Anton-Culver et al, 2000	Population-based (US)	O	N	FH-NS	99	4	.	.	4.0%	.	.

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Anton-Culver et al, 2000	Population-based (US)	O	N	Avg	81	0	.	.	0.0%	.	.
Anton-Culver et al, 2000	Population-based (US)	O	N	Mod	17	3	.	.	17.6%	.	.
Anton-Culver et al, 2000	Population-based (US)	O	N	Hgh	1	1	.	.	100.0%	.	.
Antoniou et al, 2002[28]	Families with ≥ 2 breast cancers, one of which diagnosed < 50 yrs (UK)	B	N	HGH	156	21	18	39	13.5%	11.5%	25.0%
Boyd et al, 2000[154]	Consecutive series from cancer center (US) Jewish	O	Y	FH-NS	189	67	21	88	35.4%	11.1%	46.6%
Boyd et al, 2000	Consecutive series from cancer center (US) Jewish, age: < 40	O	Y	FH-NS	7	4	0	4	57.1%	0.0%	57.1%
Boyd et al, 2000	Consecutive series from cancer center (US) Jewish, age: 40-49	O	Y	FH-NS	38	21	4	25	55.3%	10.5%	65.8%
Boyd et al, 2000	Consecutive series from cancer center (US) Jewish, age: 50-59	O	Y	FH-NS	28	14	1	15	50.0%	3.6%	53.6%
Boyd et al, 2000	Consecutive series from cancer center (US) Jewish, age: 60-69	O	Y	FH-NS	68	19	11	30	27.9%	16.2%	44.1%
Boyd et al, 2000	Consecutive series from cancer center (US) Jewish, age: > 70	O	Y	FH-NS	48	9	5	14	18.8%	10.4%	29.2%
Couch et al, 1997[31]	Familial breast cancer clinic (US) Age: <40 yrs	B	N	FH-NS	94	12	.	.	12.8%	.	.

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Couch et al, 1997	Familial breast cancer clinic (US) Age: <35 yrs and FH	B	N	Hgh	169	27	.	.	16.0%	.	.
Couch et al, 1997	Familial breast cancer clinic (US) Age: <35 yrs and FH	B	N	Hgh	5	1	.	.	20.0%	.	.
Couch et al, 1997	Familial breast cancer clinic (US) Age: 35-39 yrs and FH	B	N	Hgh	27	7	.	.	25.9%	.	.
Couch et al, 1997	Familial breast cancer clinic (US) Age: 40-44 yrs and FH	B	N	Hgh	32	5	.	.	15.6%	.	.
Couch et al, 1997	Familial breast cancer clinic (US) Age: 45-49 yrs and FH	B	N	Hgh	24	5	.	.	20.8%	.	.
Couch et al, 1997	Familial breast cancer clinic (US) Age: 50-54 yrs and FH	B	N	Hgh	34	4	.	.	11.8%	.	.
Couch et al, 1997	Familial breast cancer clinic (US) Age: 55 - 59 yrs and FH	B	N	Hgh	24	1	.	.	4.2%	.	.
Couch et al, 1997	Familial breast cancer clinic (US) Age: >59 yrs and FH	B	N	Hgh	23	4	.	.	17.4%	.	.
Eccles et al, 1998[141]	Clinically selected group (UK) Age: <40	B	N	FH-NS	155	10	.	.	6.5%	.	.

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Eccles et al, 1998	Clinically selected group (UK) Age: <40 and No FH	B	N	Avg	86	1	.	.	1.2%	.	.
Eccles et al, 1998	Clinically selected group (UK) Age: <40 and strong FH	B	N	Hgh	40	9	.	.	22.5%	.	.
Eccles et al, 1998	Clinically selected group (UK) Age: >40 and bilateral cancer	B	N	Avg	45	0	.	.	0.0%	.	.
Eccles et al, 1998	Clinically selected group (UK) Strong FH	B	N	Hgh	30	8	.	.	26.7%	.	.
Eccles et al, 1998	Clinically selected group (UK) Strong FH	O	N	Hgh	16	7	.	.	43.8%	.	.
FitzGerald et al, 1996[150]	Breast cancer referral centers (US) Jewish, age: 30-40	B	Y	FH-NS	35	6	.	.	17.1%	.	.
FitzGerald et al, 1996	Breast cancer referral centers (US) Jewish, age: ≤ 30	B	Y	FH-NS	4	2	.	.	50.0%	.	.
FitzGerald et al, 1996	Breast-cancer referral centers (US) Jewish, age: ≤ 40	B	Y	Hgh	15	4	.	.	26.7%	.	.
FitzGerald et al, 1996	Breast-cancer referral centers (US) Jewish, age: ≤ 40	B	Y	Mod	24	4	.	.	16.7%	.	.

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
FitzGerald et al, 1996	Breast cancer referral centers (US) Non-AJ, age: <30	B	N	FH-NS	26	2	.	.	7.7%	.	.
Fodor et al, 1998[125]	Hospital-based (US) AJ	B	Y	FH-NS	268	.	.	18	.	.	6.7%
Fodor et al, 1998	Hospital-based (US) AJ	B	Y	Mod	212	.	.	14	.	.	6.6%
Fodor et al, 1998	Hospital-based (US) AJ	B	Y	Hgh	50	.	.	4	.	.	8.0%
Frank et al, 1998[94]	Referred population (US) Ethnicity nonselected Age: < 50	B	N	Mod	200	47	23	70	23.5%	11.5%	35.0%
Frank et al, 1998	Referred population (US) Ethnicity nonselected Age: 20 - 29	B	N	Mod	10	5	1	6	50.0%	10.0%	60.0%
Frank et al, 1998	Referred population (US) Ethnicity nonselected Age: 30-39	B	N	Mod	80	25	7	32	31.3%	8.8%	40.0%
Frank et al, 1998	Referred population (US) Ethnicity nonselected Age: 40-49	B	N	Mod	110	17	15	32	15.5%	13.6%	29.1%
Frank et al, 1998	Referred population (US) Ethnicity nonselected	O	N	Mod	22	8	2	10	36.4%	9.1%	45.5%
Frank et al, 2002[33]	Clinical consecutive samples (US) Non-AJ	B	N	Hgh	2,549	.	.	489	.	.	19.2%

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Frank et al, 2002	Clinical consecutive samples (US) Non-AJ, age: > 50	B	N	Hgh	661	.	.	61	.	.	9.2%
Frank et al, 2002	Clinical consecutive samples (US) Non-AJ, age: 40 - 49	B	N	Hgh	1,026	.	.	161	.	.	15.7%
Frank et al, 2002	Clinical consecutive samples (US) Non-AJ, age: < 40	B	N	Hgh	862	.	.	267	.	.	31.0%
Frank et al, 2002	Clinical consecutive samples (US) Non-AJ	O	N	Hgh	294	.	.	106	.	.	36.1%
Frank et al, 2002	Clinical consecutive samples (US) Non-AJ, age: > 50	O	N	Hgh	164	.	.	53	.	.	32.3%
Frank et al, 2002	Clinical consecutive samples (US) Non-AJ, age: < 50	O	N	Hgh	130	.	.	53	.	.	40.8%
Frank et al, 2002	Clinical consecutive samples (US) AJ	B	Y	Hgh	904	.	.	195	.	.	21.6%
Frank et al, 2002	Clinical consecutive samples (US) AJ, age: > 50	B	Y	Hgh	326	.	.	36	.	.	11.0%
Frank et al, 2002	Clinical consecutive samples (US) AJ, age: 40-49	B	Y	Hgh	390	.	.	88	.	.	22.6%

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Frank et al, 2002	Clinical consecutive samples (US) AJ, age: < 40	B	Y	Hgh	188	.	.	71	.	.	37.8%
Frank et al, 2002	Clinical consecutive samples (US) AJ	O	Y	Hgh	109	.	.	44	.	.	40.4%
Frank et al, 2002	Clinical consecutive samples (US) AJ, age: > 50	O	Y	Hgh	58	.	.	24	.	.	41.4%
Frank et al, 2002	Clinical consecutive samples (US) AJ, age: < 50	O	Y	Hgh	51	.	.	20	.	.	39.2%
Gayther et al, 1999[149]	Families with ovarian cancer (UK) FH: ≥ 2 Ovarian cancer	O	N	Hgh	112	40	8	48	35.7%	7.1%	42.9%
Gershoni-Baruch et al, 2000[151]	AJ woman with family early-onset breast cancer (Israel) Age: <42	B	Y	FH-NS	172	42	13	54	24.4%	7.6%	31.4%
Gershoni-Baruch et al, 2000	AJ woman with family early-onset breast cancer (Israel) Age: <42 yrs	B	Y	Hgh	79	36	10	45	45.6%	12.7%	57.0%
Gershoni-Baruch et al, 2000	AJ woman with family early-onset breast cancer (Israel) Age: <42 yrs	B	Y	Mod	93	6	3	9	6.5%	3.2%	9.7%
Hartge et al, 1999[86]	Population-based (US) AJ	B	Y	FH-NS	297	.	.	27	.	.	9.1%

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Hartge et al, 1999	Population-based (US) AJ	B	Y	Hgh	95	.	.	13	.	.	13.7%
Hartge et al, 1999	Population-based (US) AJ	B	Y	Mod	204	.	.	14	.	.	6.9%
Hartge et al, 1999	Population-based (US) AJ, age: < 40 yrs	B	Y	FH-NS	34	.	.	9	.	.	26.5%
Hartge et al, 1999	Population-based (US) AJ, age: < 40 yrs FH	B	Y	Hgh	8	.	.	3	.	.	37.5%
Hartge et al, 1999	Population-based (US) AJ, age: < 40 yrs Non-FH	B	Y	Mod	28	.	.	6	.	.	21.4%
Hartge et al, 1999	Population-based (US) AJ, age: 40-49 yrs	B	Y	FH-NS	109	.	.	11	.	.	10.1%
Hartge et al, 1999	Population-based (US) AJ, age: 40-49 years FH	B	Y	Hgh	36	.	.	6	.	.	16.7%
Hartge et al, 1999	Population-based (US) AJ, age: 40-49 years Non-FH	B	Y	Mod	73	.	.	5	.	.	6.8%
Hartge et al, 1999	Population-based (US) AJ, age: 50-59 yrs	B	Y	FH-NS	82	.	.	6	.	.	7.3%
Hartge et al, 1999	Population-based (US) AJ, age: 50-59 years FH	B	Y	Hgh	26	.	.	4	.	.	15.4%
Hartge et al, 1999	Population-based (US) AJ, age: 50-59 years Non-FH	B	Y	Mod	56	.	.	2	.	.	3.6%

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Hartge et al, 1999	Population-based (US) AJ, age: > 60 yrs	B	Y	FH-NS	72	.	.	1	.	.	1.4%
Hartge et al, 1999	Population-based (US) AJ, age: > 60 yrs FH	B	Y	Hgh	25	.	.	0	.	.	0.0%
Hartge et al, 1999	Population-based (US) AJ, age: > 60 yrs Non-FH	B	Y	Mod	47	.	.	1	.	.	2.1%
Hopper et al, 1999[132]	Population-based (Australia) Breast cancer diagnosed <40 yrs	B	N	FH-NS	388	9	9	18	2.3%	2.3%	4.6%
Janezic et al, 1999[148]	Population-based (US)	O	N	FH-NS	107	2	.	.	1.9%	.	.
King et al, 2003[134]	Cancer centers (US) AJ	B	Y	FH-NS	1,008	67	36	103	6.9%	3.7%	10.3%
King et al, 2003	Cancer centers (US) AJ, age < 40 yrs	B	Y	FH-NS	105	26	11	37	24.0%	10.0%	35.0%
King et al, 2003	Cancer centers (US) AJ, age: 40-44 yrs	B	Y	FH-NS	135	12	10	22	9.0%	7.0%	16.0%
King et al, 2003	Cancer centers (US) AJ, age: 45-49 yrs	B	Y	FH-NS	187	11	4	15	6.0%	2.0%	8.0%
King et al, 2003	Cancer centers (US) AJ, age: 50-59 yrs	B	Y	FH-NS	305	15	6	21	5.0%	2.0%	7.0%
King et al, 2003	Cancer centers (US) AJ, age: > 60 yrs	B	Y	FH-NS	276	2	6	8	0.8%	2.0%	2.8%
King et al, 2003	Cancer centers (US) AJ, age: 40-49 yrs	B	Y	FH-NS	322	23	14	37	7.1%	4.3%	11.5%

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
King et al, 2003	Cancer centers (US) AJ, FH with breast cancer	B	Y	Hgh	350	34	16	50	9.7%	4.6%	14.3%
King et al, 2003	Cancer centers (US) AJ, Non - FH in 1 degree relatives	B	Y	Mod	658	33	20	53	5.0%	3.0%	8.0%
Langston et al, 1996[142]	Population-based (US) Age: < 35 yrs	B	N	FH-NS	80	6	.	.	7.5%	.	.
Langston et al, 1996	Population-based (US) Age: < 35 yrs; FH	B	N	Mod	41	4	.	.	9.8%	.	.
Langston et al, 1996	Population-based (US) Age: < 35 yrs; Non-FH	B	N	Avg	39	2	.	.	5.1%	.	.
Malone et al, 2000[143]	Population-based (US) Age: < 35 yrs	B	N	FH-NS	203	12	7	19	5.9%	3.4%	9.4%
Malone et al, 2000	Population-based (US) Age: < 30 yrs	B	N	FH-NS	45	5	2	7	11.1%	4.4%	15.6%
Malone et al, 2000	Population-based (US) Age: 30-34 yrs	B	N	FH-NS	158	7	5	12	4.4%	3.2%	7.6%
Malone et al, 2000	Population-based (US) Age: < 35 yrs, Non-FH	B	N	Avg	104	2	1	3	1.9%	1.0%	2.9%
Malone et al, 2000	Population-based (US) Age: < 35 yrs, FH	B	N	Mod	38	4	1	5	10.5%	2.6%	13.2%
Malone et al, 2000	Population-based (US) Age: < 35 yrs, FH	B	N	Hgh	4	1	2	3	25.0%	50.0%	75.0%
Malone et al, 2000	Population-based (US) Age: < 45 yrs, FH: 1st-degree	B	N	Mod and Hgh combined	225	16	11	27	7.1%	4.9%	12.0%

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Malone et al, 2000	Population-based (US) Age: < 45 yrs, FH: 1st-degree	B	N	Mod	206	14	7	21	6.8%	3.4%	10.2%
Malone et al, 2000	Population-based (US) Age: < 45 yrs, FH: ≥ 1st-degree breast cancer	B	N	Hgh	19	2	4	6	10.5%	21.1%	31.6%
Modan et al, 2001[127]	Population based case-control study (Israel) AJ	O	Y	FH-NS	596	182	64	244	30.5%	10.7%	40.9%
Moslehi et al, 2000[135]	Hospital-based (N. America /Israel) AJ	O	Y	FH-NS	208	57	29	86	27.4%	13.9%	41.3%
Moslehi et al, 2000	Hospital-based (N. America /Israel) AJ, Non-FH	O	Y	Mod	119	23	10	33	19.3%	8.4%	27.7%
Moslehi et al, 2000	Hospital-based (N. America /Israel) AJ, FH	O	Y	Hgh	80	34	17	51	42.5%	21.3%	63.8%
Moslehi et al, 2000	Hospital-based (N. America /Israel) AJ, age: < 40 yrs	O	Y	FH-NS	18	7	1	8	46.7%	6.7%	53.3%
Moslehi et al, 2000	Hospital-based (N. America /Israel) AJ, age: 40-49 yrs	O	Y	FH-NS	54	24	2	26	44.4%	3.7%	48.1%
Moslehi et al, 2000	Hospital-based (N. America /Israel) AJ, age: 50-59 yrs	O	Y	FH-NS	43	15	8	23	34.9%	18.6%	53.5%

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Moslehi et al, 2000	Hospital-based (N. America /Israel) AJ, age: 60-69 yrs	O	Y	FH-NS	49	9	10	19	18.4%	20.4%	38.8%
Moslehi et al, 2000	Hospital-based (N. America /Israel) AJ, age: > 70 yrs	O	Y	FH-NS	44	2	8	10	4.5%	18.2%	22.7%
Newman et al, 1998[145]	Population-based (US) Breast cancer, age: 20-74 yrs	B	N	FH-NS	211	3	.	.	1.4%	.	.
Newman et al, 1998	Population-based (US) Breast cancer, age: 20-74 yrs, white Adjusted for sampling probabilities	B	N	FH-NS	211	7	.	.	3.3%	.	.
Oddoux et al, 1996[128]	Cancer center study (US) AJ with FH, age: 20-80 yrs	B	Y	Hgh	107	28	7	35	26.2%	6.5%	32.7%
Oddoux et al, 1996	Cancer center study (US) AJ with FH, age: < 42 yrs	B	Y	Hgh	61	16	4	20	26.2%	6.6%	32.8%
Oddoux et al, 1996	Cancer center study (US) AJ with FH, age: > 42 yrs	B	Y	Hgh	46	12	3	15	26.1%	6.5%	32.6%
Peto et al, 1999[29]	Population-based Case Control Studies (UK) Age: <46 yrs	B	N	FH-NS	617	16	14	30	2.6%	2.3%	4.9%

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Peto et al, 1999	Population-based Case Control Studies (UK) Age: <46 yrs	B	N	Avg	547	13	13	26	2.4%	2.4%	4.8%
Peto et al, 1999	Population-based Case Control Studies (UK) Age: <46 yrs	B	N	Mod	67	3	0	3	3.0%	0.0%	4.5%
Peto et al, 1999	Population-based Case Control Studies (UK) Age: <46 yrs	B	N	Hgh	3	0	1	1	0.0%	33.3%	33.3%
Peto et al, 1999	Population-based Case Control Studies (UK) Age: <36 yrs	B	N	FH-NS	254	9	6	15	3.5%	2.4%	5.9%
Peto et al, 1999	Population-based Case Control Studies (UK) Age: 36-45 yrs	B	N	FH-NS	363	7	8	15	1.9%	2.2%	4.1%
Risch et al, 2001[133]	Population-based (Canada) Age: 20-79 yrs	O	N	FH-NS	649	39	21	60	6.0%	3.2%	9.2%
Risch et al, 2001	Population-based (Canada) Non-FH	O	N	Avg	504	10	12	22	2.0%	2.4%	4.4%
Risch et al, 2001	Population-based (Canada) FH	O	N	Mod	145	29	9	27	20.0%	6.2%	18.6%

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Risch et al, 2001	Population-based (Canada) Age: ≤ 40 yrs	O	N	FH-NS	96	3	1	4	3.1%	1.0%	4.2%
Risch et al, 2001	Population-based (Canada) Age: 41-50 yrs	O	N	FH-NS	136	21	4	25	15.4%	2.9%	18.4%
Risch et al, 2001	Population-based (Canada) Age: 51-60 yrs	O	N	FH-NS	165	9	7	16	5.5%	4.2%	9.7%
Risch et al, 2001	Population-based (Canada) Age: > 60 yrs	O	N	FH-NS	252	6	9	15	2.4%	3.6%	6.0%
Risch et al, 2001	Population-based (Canada) AJ ethnicity	O	Y	FH-NS	19	4	1	5	21.1%	5.3%	26.3%
Robson et al, 1998[153]	Hospital-based (US) Jewish, breast cancer diagnosed < 42 yrs	B	Y	FH-NS	91	23	7	30	25.3%	7.7%	33.0%
Robson et al, 1998	Hospital-based (US) Jewish, breast cancer diagnosed < 42 yrs	B	Y	Hgh	66	.	.	27	.	.	40.9%
Robson et al, 1998	Hospital-based (US) Jewish, breast cancer diagnosed < 42 yrs	B	Y	Mod	25	.	.	3	.	.	12.0%
Satagopan et al, 2001[137]	Hospital-based Memorial Hospital (NY) AJ	B	Y	FH-NS	305	22	7	29	7.2%	2.3%	9.5%

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Satagopan et al, 2001	Hospital-based Memorial Hospital (NY) AJ, age: < 40 yrs	B	Y	FH-NS	28	8	0	8	28.6%	0.0%	28.6%
Satagopan et al, 2001	Hospital-based Memorial Hospital (NY) AJ, age: 40-49 yrs	B	Y	FH-NS	66	8	2	10	12.1%	3.0%	15.2%
Satagopan et al, 2001	Hospital-based Memorial Hospital (NY) AJ, age: > 50 yrs	B	Y	FH-NS	211	6	5	11	2.8%	2.4%	5.2%
Satagopan et al, 2001	Hospital-based Mount Sinai (NY) AJ	B	Y	FH-NS	268	10	8	18	3.7%	3.0%	6.7%
Satagopan et al, 2001	Hospital-based Mount Sinai (NY) AJ, age: < 40 yrs	B	Y	FH-NS	15	1	1	2	6.7%	6.7%	13.3%
Satagopan et al, 2001	Hospital-based Mount Sinai (NY) AJ, age: 40-49 yrs	B	Y	FH-NS	82	3	3	6	3.7%	3.7%	7.3%
Satagopan et al, 2001	Hospital-based Mount Sinai (NY) AJ, age: > 50 yrs	B	Y	FH-NS	171	6	4	10	3.5%	2.3%	5.8%
Satagopan et al, 2001	Hospital-based Montreal (Canada) AJ	B	Y	FH-NS	209	25	8	33	12.0%	3.8%	15.8%
Satagopan et al, 2001	Hospital-based Montreal (Canada) AJ , Age: < 40 yrs	B	Y	FH-NS	28	9	1	10	32.1%	3.6%	35.7%

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Satagopan et al, 2001	Hospital-based Montreal (Canada) AJ, age: 40-49 yrs	B	Y	FH-NS	56	8	1	9	14.3%	1.8%	16.1%
Satagopan et al, 2001	Hospital-based Montreal (Canada) AJ , age: > 50 yrs	B	Y	FH-NS	125	8	6	14	6.4%	4.8%	11.2%
Stratton et al, 1997[147]	Hospital-based (UK) < 70 yrs	O	N	FH-NS	374	12	.	.	3.2%	.	.
Stratton et al, 1997	Hospital-based (UK) < 70 yrs, Non-FH of ovarian cancer	O	N	Avg	345	6	.	.	1.7%	.	.
Stratton et al, 1997	Hospital-based (UK) < 70 yrs, FH of Ovarian cancer	O	N	Mod	29	6	.	.	20.7%	.	.
Struewing et al, 1997[11]	Population - based (US) AJ, age: > 20 yrs	B	Y	FH-NS	296	16	11	27	5.4%	3.7%	9.1%
Struewing et al, 1997	Population - based (US) AJ, age: < 50 yrs	B	Y	FH-NS	143	12	8	20	8.4%	5.6%	14.0%
Struewing et al, 1997	Population - based (US) AJ, age: ≥ 50 yrs	B	Y	FH-NS	153	4	3	7	2.6%	2.0%	4.6%
Sutcliffe et al, 2000[146]	UKCCCR Familial Ovarian Cancer Register FH: ≥ 2 ovarian cancers	B	N	Hgh	112	.	.	55	.	.	49.1%
Warner et al, 1999[138]	Hospital-based (Canada) AJ	B	Y	FH-NS	412	34	15	48	8.3%	3.6%	11.7%
Warner et al, 1999	Hospital-based (Canada) AJ, age: 20-29 yrs	B	Y	FH-NS	3	1	0	1	33.3%	0.0%	33.3%

Appendix J. Evidence Table of Studies of Prevalence of Mutation Among Breast or Ovarian Cancer Cases

Author, year	Population	Cancer	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Warner et al, 1999	Hospital-based (Canada) AJ, age: 30-39 yrs	B	Y	FH-NS	27	10	2	12	37.0%	7.4%	44.4%
Warner et al, 1999	Hospital-based (Canada) AJ, age: 40-49 yrs	B	Y	FH-NS	134	16	8	23	11.9%	6.0%	17.2%
Warner et al, 1999	Hospital-based (Canada) AJ, age: 50-59 yrs	B	Y	FH-NS	111	5	4	9	4.5%	3.6%	8.1%
Warner et al, 1999	Hospital-based (Canada) AJ, age: > 60 yrs	B	Y	FH-NS	137	2	1	3	1.5%	0.7%	2.2%
Warner et al, 1999	Hospital-based (Canada) AJ, Non-FH	B	Y	Mod	273	11	4	15	4.0%	1.5%	5.5%

AJ, Ashkenazi Jewish; FH, family history; FH-NS, family history non-selected; UKCCCR, United Kingdom Coordinating Committee on Cancer Research.

* Average risk (Avg), no first-degree relatives with breast or ovarian cancer; moderate risk (Mod), one first-degree relative with cancer or AJ without a first-degree relative with cancer; high risk (Hgh), two or more first-degree relatives with cancer or AJ with one or more first-degree relatives with breast or ovarian cancer.

Appendix K. Evidence Table of Studies of Prevalence of Mutation Among Controls Without Breast or Ovarian Cancer

Author, year	Population	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Fodor et al, 1998[125]	Referral for prenatal carrier testing (NY) AJ	Y	FH-NS	1,715	20	18	38	1.2%	1.0%	2.2%
Frank et al, 2002[33]	Clinical consecutive samples (US) Non-AJ, no cancer, non-FH	N	Hgh	1,706	.	.	148	.	.	8.7%
Frank et al, 2002	Clinical consecutive samples (US) AJ, no cancer, non-FH	Y	Hgh	1,176	.	.	196	.	.	16.7%
Hartge et al, 1999[86]	Population-based (US) AJ	Y	FH-NS	3,419	.	.	59	.	.	1.7%
Hartge et al, 1999	Population-based (US) AJ, age: < 40 yrs	Y	Hgh	783	.	.	30	.	.	3.8%
Hartge et al, 1999	Population-based (US) AJ, age: < 40 yrs	Y	Mod	2,636	.	.	32	.	.	1.2%
Hartge et al, 1999	Population-based (US) AJ, age: < 40 yrs	Y	FH-NS	690	.	.	19	.	.	2.8%
Hartge et al, 1999	Population-based (US) AJ, age: < 40 yrs, FH	Y	Hgh	137	.	.	10	.	.	7.3%
Hartge et al, 1999	Population-based (US) AJ, age: < 40 yrs, non-FH	Y	Mod	553	.	.	9	.	.	1.6%
Hartge et al, 1999	Population-based (US) AJ, age: 40-49 yrs	Y	FH-NS	1,112	.	.	23	.	.	2.1%
Hartge et al, 1999	Population-based (US) AJ, age: 40-49 yrs, FH	Y	Hgh	249	.	.	12	.	.	4.8%
Hartge et al, 1999	Population-based (US) AJ, age: 40-49 yrs, non-FH	Y	Mod	863	.	.	11	.	.	1.3%

Appendix K. Evidence Table of Studies of Prevalence of Mutation Among Controls Without Breast or Ovarian Cancer

Author, year	Population	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Hartge et al, 1999	Population-based (US) AJ, age: 50-59 yrs	Y	FH-NS	811	.	.	14	.	.	1.7%
Hartge et al, 1999	Population-based (US) AJ, age: 50-59 yrs, FH	Y	Hgh	192	.	.	6	.	.	3.1%
Hartge et al, 1999	Population-based (US) AJ, age: 50-59 yrs, non-FH	Y	Mod	619	.	.	8	.	.	1.3%
Hartge et al, 1999	Population-based (US) AJ, age: > 60 yrs	Y	FH-NS	806	.	.	6	.	.	0.7%
Hartge et al, 1999	Population-based (US) AJ, age: > 60 yrs, FH	Y	Hgh	205	.	.	2	.	.	1.0%
Hartge et al, 1999	Population-based (US) AJ, age: > 60 yrs, non-FH	Y	Mod	601	.	.	4	.	.	0.7%
Liede et al, 2002[129]	Healthy Jewish women with a FH of breast or ovarian cancer; exclude incident breast and ovarian cancer (US)	Y	Hgh	213	31	2	33	14.6%	0.9%	15.5%
Liede et al, 2002	Healthy Jewish women with a FH of breast or ovarian cancer; exclude incident breast and ovarian cancer (US)	Y	Hgh	199	19	2	21	9.5%	1.0%	10.6%
Malone et al, 2000[143]	Population-based (US) Age: < 45 yrs, FH: 1st-degree of ≥ 4 breast cancers	N	Mod	71	0	0		0.0%	0.0%	
Modan et al, 2001[127]	Population-based (Israel) AJ	Y	FH-NS	751	3	10	13	0.4%	1.3%	1.7%
Oddoux et al, 1996[128]	Population-based (US) AJ, NYU Medical Center	Y	FH-NS	848	.	8	.	.	0.9%	.

Appendix K. Evidence Table of Studies of Prevalence of Mutation Among Controls Without Breast or Ovarian Cancer

Author, year	Population	AJ	Risk for mutation*	N tested	N *BRCA1* positive	N *BRCA2* positive	N *BRCA1* or *BRCA2* positive	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Oddoux et al, 1996	Population-based (US) AJ, NIH	Y	FH-NS	407	.	4	.	.	0.9%	.
Roa et al, 1996[12]	Population-based AJ	Y	FH-NS	3,116	38	47	85	1.2%	1.5%	2.7%
Satagopan et al, 2001[137]	Population-based (US) AJ	Y	FH-NS	3,434	32	30	62	0.9%	0.9%	1.8%
Satagopan et al, 2001	Population-based (US) AJ, age: < 40 yrs	Y	FH-NS	692	11	8	19	1.6%	1.2%	2.7%
Satagopan et al, 2001	Population-based (US) AJ, age: 40-49 yrs	Y	FH-NS	1,113	12	11	23	1.1%	1.0%	2.1%
Satagopan et al, 2001	Population-based (US) AJ, age: > 50 yrs	Y	FH-NS	1,629	9	11	20	0.6%	0.7%	1.2%
Struewing et al, 1995[126]	Unselected for breast cancer or AJ, FH	Y	FH-NS	858	8	.	.	0.9%	.	.
Struewing et al, 1997[11]	Population-based (US) AJ, age: > 20 yrs	Y	FH-NS	3,440	32	30	62	0.9%	0.9%	1.8%
Struewing et al, 1997	Population-based (US) AJ, non-FH	Y	Mod	2,648	11	21	32	0.4%	0.8%	1.2%
Struewing et al, 1997	Population-based (US) AJ, FH	Y	Hgh	786	21	9	30	2.7%	1.1%	3.8%

AJ, Ashkenazi Jewish; FH, family history; FH-NS - family history non-selected; NIH, National Institutes of Health.

* Average risk, no first-degree relatives with breast or ovarian cancer; moderate risk (Mod), one first-degree relative with cancer or AJ without a first-degree relative with cancer; high risk (Hgh), two or more first-degree relatives with cancer or AJ with one or more first-degree relatives with breast or ovarian cancer.

Appendix L. Evidence Table of Penetrance Studies

Author, year	Population or risk group	N	Risk to age:	Breast cancer risk *BRCA1* (%, 95% CI)	Breast cancer risk *BRCA2* (%, 95% CI)	Breast cancer risk *BRCA1* or *BRCA2* (%, 95% CI)	Breast cancer risk mutation negative (%, 95% CI)
Anglian BC Study Group, 2000[27]	Breast cancer diagnosed < 55	8 families of *BRCA1* mutations 16 families of *BRCA2* mutations	40 yrs	20 (0-50)	6 (0-17)	10 (0-21)	.
Anglian BC Study Group, 2000	Breast cancer diagnosed < 55	8 families of *BRCA1* mutations 16 families of *BRCA2* mutations	50 yrs	32 (2-62)	18 (2-32)	21 (5-34)	.
Anglian BC Study Group, 2000	Breast cancer diagnosed < 55	8 families of *BRCA1* mutations 16 families of *BRCA2* mutations	60 yrs	46 (3-82)	31 (3-53)	34 (5-55)	.
Anglian BC Study Group, 2000	Breast cancer diagnosed < 55	8 families of *BRCA1* mutations 16 families of *BRCA2* mutations	70 yrs	47 (5-82)	56 (5-80)	54 (14-76)	.
Anglian BC Study Group, 2000	Breast cancer diagnosed < 55	8 families of *BRCA1* mutations 16 families of *BRCA2* mutations	80 yrs	48 (7-82)	74 (7-94)	69 (11-90)	.
Antoniou et al, 2003[130]	Meta-analysis of studies that included 1st degree relatives of breast cancer prevalent and incident and/or ovarian cancer prevalent and incident cases positive for a *BRCA1* or *BRCA2* mutation	280 families of *BRCA1*+ 218 families of *BRCA2*+	70 yrs	65 (51-75)	45 (33-54)	.	.

Appendix L. Evidence Table of Penetrance Studies

Author, year	Relative risk breast cancer (95% CI)	General population's risk breast cancer	Ovarian cancer risk *BRCA1* (%, 95% CI)	Ovarian cancer risk *BRCA2* (%, 95% CI)	Ovarian cancer risk *BRCA1* or *BRCA2* (%, 95% CI)	Ovarian cancer risk mutation negative (%, 95% CI)	Relative risk ovarian cancer (95% CI)	General population's risk ovarian cancer
Anglian BC Study Group, 2000[27]	.	0.4	3 (0-30)	1 (0-5)	1 (0-5)	.	.	0.1
Anglian BC Study Group, 2000	.	1.5	11 (1-74)	3 (0-19)	4 (1-18)	.	.	0.3
Anglian BC Study Group, 2000	.	3.1	24 (2-96)	6 (1-39)	10 (2-37)	.	.	0.7
Anglian BC Study Group, 2000	.	5.0	36 (4-99)	10 (1-55)	16 (4-51)	.	.	1.0
Anglian BC Study Group, 2000	.		47 (5-100)	14 (2-68)	22 (6-65)	.	.	
Antoniou et al, 2003[130]	.		39 (22-51)	11 (4.1-18)	.	.	.	

Appendix L. Evidence Table of Penetrance Studies

Author, year	Population or risk group	N	Risk to age:	Breast cancer risk *BRCA1* (%, 95% CI)	Breast cancer risk *BRCA2* (%, 95% CI)	Breast cancer risk *BRCA1* or *BRCA2* (%, 95% CI)	Breast cancer risk mutation negative (%, 95% CI)
Antoniou et al, 2003	Above, case with early-onset breast cancer (<35)	* families of *BRCA1* + 46 families of *BRCA2* + *not stated	70 yrs	87 (67-95)	55 (16-76)	.	.
Antoniou et al, 2003	Above, case with older-onset breast cancer (≥35)	* families of *BRCA1* + 102 families of *BRCA* 2+ *not stated	70 yrs	61 (41-74)	49 (32-61)	.	.
Antoniou et al, 2003	Above, case with ovarian cancer	117 families of *BRCA1* + 50 families of *BRCA2* +	70 yrs	56	.	.	.
Antoniou et al, 2002[28]	Breast cancer diagnosed < 55 Multiple case families, ads and referrals	21 *BRCA1* + 18 *BRCA2*+	30-39	12.9	8.3	.	0.4
Antoniou et al, 2002	Breast cancer diagnosed < 55 Multiple case families, ads and referrals	21 *BRCA1* + 18 *BRCA2*+	40-49	26.2	20.7	.	1.5
Antoniou et al, 2002	Breast cancer diagnosed < 55 Multiple case families, ads and referrals	21 *BRCA1* + 18 *BRCA2*+	50-59	32.1	35.3	.	3.0
Antoniou et al, 2002	Breast cancer diagnosed < 55 Multiple case families, ads and referrals	21 *BRCA1* + 18 *BRCA2*+	60-69	35.3	50.3	.	4.9

Appendix L. Evidence Table of Penetrance Studies

Author, year	Relative risk breast cancer (95% CI)	General population's risk breast cancer	Ovarian cancer risk *BRCA1* (%, 95% CI)	Ovarian cancer risk *BRCA2* (%, 95% CI)	Ovarian cancer risk *BRCA1* or *BRCA2* (%, 95% CI)	Ovarian cancer risk mutation negative (%, 95% CI)	Relative risk ovarian cancer (95% CI)	General population's risk ovarian cancer
Antoniou et al, 2003	.		51 (9.1-73)	35 (0.61*) *typo in paper	.	.	.	
Antoniou et al, 2003	.	.	32 (11-49)	3 (0-7)	.	.	.	.
Antoniou et al, 2003	.	.	.	.	.	.	.	.
Antoniou et al, 2002[28]	.	.	0.4	0.3	.	0.1	.	.
Antoniou et al, 2002	.	.	11.4	0.8	.	0.2	.	.
Antoniou et al, 2002	.	.	18.3	5.2	.	0.6	.	.
Antoniou et al, 2002	.	.	25.9	9.1	.	1.0	.	.

Appendix L. Evidence Table of Penetrance Studies

Author, year	Population or risk group	N	Risk to age:	Breast cancer risk *BRCA1* (%, 95% CI)	Breast cancer risk *BRCA2* (%, 95% CI)	Breast cancer risk *BRCA1* or *BRCA2* (%, 95% CI)	Breast cancer risk mutation negative (%, 95% CI)
Brose et al, 2002[21]	Seek breast cancer counseling, documented *BRCA1* mutation	147 *BRCA1*	70	78.3 (74.1-82.4)	.	.	.
Ford et al, 1998[131]	4 or more cases of female breast cancer diagnosed < 60 or male breast cancer diagnosed at any age	64 *BRCA1*+ *32 BRCA2*+	30	3.6 (0-14)	0.6 (0-19)	.	.
Ford et al, 1998	4 or more cases of female breast cancer diagnosed < 60 or male breast cancer diagnosed at any age	64 *BRCA1*+ *32 BRCA2*+	40	18 (0-35)	12 (0-24)	.	.
Ford et al, 1998	4 or more cases of female breast cancer diagnosed < 60 or male breast cancer diagnosed at any age	64 *BRCA1*+ *32 BRCA* 2+	50	49 (28-64)	28 (9-44)	.	.
Ford et al, 1998	4 or more cases of female breast cancer diagnosed < 60 or male breast cancer diagnosed at any age	64 *BRCA1*+ *32 BRCA2*+	60	64 (43-77)	18 (22-65)	.	.
Ford et al, 1998	4 or more cases of female breast cancer diagnosed < 60 or male breast cancer diagnosed at any age	64 *BRCA1*+ *32 BRCA2*+	70	71 (53-82)	84 (43-95)	.	.
Hopper et al, 1999[132]	Population-based, breast cancer diagnosed < 40	9 *BRCA1* + 9 *BRCA2*+	40	.	.	8 (0-20)	.
Hopper et al, 1999	Population-based, breast cancer diagnosed < 40	9 *BRCA1* + 9 *BRCA2*+	50	.	.	10 (0-24)	.

Appendix L. Evidence Table of Penetrance Studies

Author, year	Relative risk breast cancer (95% CI)	General population's risk breast cancer	Ovarian cancer risk *BRCA1* (%, 95% CI)	Ovarian cancer risk *BRCA2* (%, 95% CI)	Ovarian cancer risk *BRCA1* or *BRCA2* (%, 95% CI)	Ovarian cancer risk mutation negative (%, 95% CI)	Relative risk ovarian cancer (95% CI)	General population's risk ovarian cancer
Brose et al, 2002[21]	.	12.9	49.9 (44.9-55.0)	.	.	.	.	1.7
Ford et al, 1998[131]	.	.	.	.	.	.	.	.
Ford et al, 1998	.	.	.	.	.	.	.	.
Ford et al, 1998	.	.	.	0.4 (0-1)	.	.	.	.
Ford et al, 1998	.	.	.	.	.	.	.	.
Ford et al, 1998	.	.	.	27 (0-47)	.	.	.	.
Hopper et al, 1999[132]	.	.	.	.	.	.	.	.
Hopper et al, 1999	.	.	.	.	.	.	.	.

Appendix L. Evidence Table of Penetrance Studies

Author, year	Population or risk group	N	Risk to age:	Breast cancer risk *BRCA1* (%, 95% CI)	Breast cancer risk *BRCA2* (%, 95% CI)	Breast cancer risk *BRCA1* or *BRCA2* (%, 95% CI)	Breast cancer risk mutation negative (%, 95% CI)
Hopper et al, 1999	Population-based, breast cancer diagnosed < 40	9 *BRCA1* + 9 *BRCA2*+	60	.	.	31 (7-56)	.
Hopper et al, 1999	Population-based, breast cancer diagnosed < 40	9 *BRCA1* + 9 *BRCA2*+	70	.	.	40 (16-64)	.
King et al, 2003[134]	New York cancer centers, breast cancer, Ashkenazi Jewish	67 *BRCA1* + 37 *BRCA2* +	30	3 (1)	0	2 (1) (SD)	.
King et al, 2003	New York cancer centers, breast cancer, Ashkenazi Jewish	67 *BRCA1* + 37 *BRCA2* +	40	21 (3)	17 (5)	20 (3)	.
King et al, 2003	New York cancer centers, breast cancer, Ashkenazi Jewish	67 *BRCA1* + 37 *BRCA2* +	50	39 (4)	34 (7)	37 (4)	.
King et al, 2003	New York cancer centers, breast cancer, Ashkenazi Jewish	67 *BRCA1* + 37 *BRCA2* +	60	58 (5)	48 (8)	55 (4)	.
King et al, 2003	New York cancer centers, breast cancer, Ashkenazi Jewish	67 *BRCA1* + 37 *BRCA2* +	70	69 (5)	74 (8)	71 (4)	.
King et al, 2003	New York cancer centers, breast cancer, Ashkenazi Jewish	67 *BRCA1* + 37 *BRCA2* +	80	81 (6)	85 (8)	82 (5)	.
Liede et al, 2002[129]	Healthy Jewish women with a family history of breast or ovarian cancer	27 *BRCA1* 185delAG 4 *BRCA1* 5382insC 2 *BRCA2* 6174delT	10-yr risk for carriers; less follow-up for non-carriers	.	.	21	< 1

Appendix L. Evidence Table of Penetrance Studies

Author, year	Relative risk breast cancer (95% CI)	General population's risk breast cancer	Ovarian cancer risk *BRCA1* (%, 95% CI)	Ovarian cancer risk *BRCA2* (%, 95% CI)	Ovarian cancer risk *BRCA1* or *BRCA2* (%, 95% CI)	Ovarian cancer risk mutation negative (%, 95% CI)	Relative risk ovarian cancer (95% CI)	General population's risk ovarian cancer
Hopper et al, 1999	.	.	.	.	.	.	.	.
Hopper et al, 1999	.	.	.	.	.	.	.	.
King et al, 2003[134]	.	.	0	0	.	.	.	.
King et al, 2003	.	.	3 (1)	2 (2)	.	.	.	.
King et al, 2003	.	.	21 (4)	2 (2)	.	.	.	.
King et al, 2003	.	.	40 (5)	6 (5)	.	.	.	.
King et al, 2003	.	.	46 (6)	12 (7)	.	.	.	.
King et al, 2003	.	.	54 (7)	23 (12)	.	.	.	.
Liede et al, 2002[129]	18 (2.1-157)	.	.	.	28	< 1	32 (4.0-260)	.

Appendix L. Evidence Table of Penetrance Studies

Author, year	Population or risk group	N	Risk to age:	Breast cancer risk *BRCA1* (%, 95% CI)	Breast cancer risk *BRCA2* (%, 95% CI)	Breast cancer risk *BRCA1* or *BRCA2* (%, 95% CI)	Breast cancer risk mutation negative (%, 95% CI)
Moslehi et al, 2000[135]	Hospital-based ovarian cancer, Ashkenazi Jewish	43 *BRCA1* 185delAG 14 *BRCA1* 5382insC 29 *BRCA2* 6174delT	55	31.3	6.1	.	.
Moslehi et al, 2000	Hospital-based ovarian cancer, Ashkenazi Jewish	43 *BRCA1* 185delAG 14 *BRCA1* 5382insC 29 *BRCA2* 6174delT	65	45.9	.	.	.
Moslehi et al, 2000	Hospital-based ovarian cancer, Ashkenazi Jewish	43 *BRCA1* 185delAG 14 *BRCA1* 5382insC 29 *BRCA2* 6174delT	75	43.8	36.8	.	.
Moslehi et al, 2000	Hospital-based ovarian cancer, Ashkenazi Jewish	43 *BRCA1* 185delAG	75	44.2	.	.	.
Moslehi et al, 2000	Hospital-based ovarian cancer, Ashkenazi Jewish	14 *BRCA1* 5382insC	75	39.3	.	.	.
Risch et al, 2001[133]	Population-based, ovarian cancer	39 *BRCA1*+ 21 *BRCA2*+	80	68		.	9.9
Satagopan et al, 2001[137]	Case series, breast cancer, Ashkenazi Jewish	57 *BRCA1*+ 23*BRCA2*+	20-29	0.6 (0.3-1.5)	0.1 (0-0.5)	.	.

Appendix L. Evidence Table of Penetrance Studies

Author, year	Relative risk breast cancer (95% CI)	General population's risk breast cancer	Ovarian cancer risk *BRCA1* (%, 95% CI)	Ovarian cancer risk *BRCA2* (%, 95% CI)	Ovarian cancer risk *BRCA1* or *BRCA2* (%, 95% CI)	Ovarian cancer risk mutation negative (%, 95% CI)	Relative risk ovarian cancer (95% CI)	General population's risk ovarian cancer
Moslehi et al, 2000[135]	.	.	.	.	.	.	.	.
Moslehi et al, 2000	.	.	.	.	.	.	.	.
Moslehi et al, 2000	.	.	.	26.6	.	.	.	.
Moslehi et al, 2000	.	.	10.1	.	.	.	.	.
Moslehi et al, 2000	.	.	21.0	.	.	.	.	.
Risch et al, 2001[133]	.	.	36	.	.	2.5	.	.
Satagopan et al, 2001[137]	.	.	.	.	.	.	.	.

Appendix L. Evidence Table of Penetrance Studies

Author, year	Population or risk group	N	Risk to age:	Breast cancer risk *BRCA1* (%, 95% CI)	Breast cancer risk *BRCA2* (%, 95% CI)	Breast cancer risk *BRCA1* or *BRCA2* (%, 95% CI)	Breast cancer risk mutation negative (%, 95% CI)
Satagopan et al, 2001	Case series, breast cancer, Ashkenazi Jewish	57 *BRCA1* + 23*BRCA2* +	30-39	7 (4-16)	1.4 (0.5-5.4)	.	.
Satagopan et al, 2001	Case series, breast cancer, Ashkenazi Jewish	57 *BRCA1* + 23*BRCA2* +	40-49	18 (12-34)	6 (2-14)	.	.
Satagopan et al, 2001	Case series, breast cancer, Ashkenazi Jewish	57 *BRCA1* + 23*BRCA2* +	50-59	31 (22-56)	15 (8-28)	.	.
Satagopan et al, 2001	Case series, breast cancer, Ashkenazi Jewish	57 *BRCA1* + 23*BRCA2* +	60-69	46 (31-80)	26 (14-50)	.	.
Satagopan et al, 2001	Case series, breast cancer, Ashkenazi Jewish	57 *BRCA1* + 23*BRCA2* +	70-79	59 (40-93)	38 (20-68)	.	.
Satagopan et al, 2001	Case series, breast cancer, Ashkenazi Jewish	57 *BRCA1* + 23*BRCA2* +	80-89	70 (47-98)	47 (26-80)	.	.
Satagopan et al, 2002[136]	Hospital-based ovarian cancer, Ashkenazi Jewish	103 *BRCA1* + 44 *BRCA2* +	20-29	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	103 *BRCA1* + 44 *BRCA2* +	30-39	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	103 *BRCA1* + 44 *BRCA2* +	40-49	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	103 *BRCA1* + 44 *BRCA2* +	50-59	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	103 *BRCA1* + 44 *BRCA2* +	60-69	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	103 *BRCA1* + 44 *BRCA2* +	70-79	.	.	.	.

Appendix L. Evidence Table of Penetrance Studies

Author, year	Relative risk breast cancer (95% CI)	General population's risk breast cancer	Ovarian cancer risk *BRCA1* (%, 95% CI)	Ovarian cancer risk *BRCA2* (%, 95% CI)	Ovarian cancer risk *BRCA1* or *BRCA2* (%, 95% CI)	Ovarian cancer risk mutation negative (%, 95% CI)	Relative risk ovarian cancer (95% CI)	General population's risk ovarian cancer
Satagopan et al, 2001	.	.	.	.	.	.	.	.
Satagopan et al, 2001	.	.	.	.	.	.	.	.
Satagopan et al, 2001	.	.	.	.	.	.	.	.
Satagopan et al, 2001	.	.	.	.	.	.	.	.
Satagopan et al, 2001	.	.	.	.	.	.	.	.
Satagopan et al, 2001	.	.	.	.	.	.	.	.
Satagopan et al, 2002[136]	.	.	1 (0-2)	0.2 (0-1)	.	.	.	.
Satagopan et al, 2002	.	.	3 (1-7)	0.7 (0-3)	.	.	.	.
Satagopan et al, 2002	.	.	11 (7-21)	3 (1-8)	.	.	.	.
Satagopan et al, 2002	.	.	23 (16-44)	11 (7-21)	.	.	.	.
Satagopan et al, 2002	.	.	37 (25-71)	21 (13-41)	.	.	.	.
Satagopan et al, 2002	.	.	52 (35-90)	32 (20-60)	.	.	.	.

Appendix L. Evidence Table of Penetrance Studies

Author, year	Population or risk group	N	Risk to age:	Breast cancer risk *BRCA1* (%, 95% CI)	Breast cancer risk *BRCA2* (%, 95% CI)	Breast cancer risk *BRCA1* or *BRCA2* (%, 95% CI)	Breast cancer risk mutation negative (%, 95% CI)
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	103 *BRCA1* + 44 *BRCA2* +	80+	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	76 *BRCA1* 185delAG	20-29	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	76 *BRCA1* 185delAG	30-39	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	76 *BRCA1* 185delAG	40-49	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	76 *BRCA1* 185delAG	50-59	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	76 *BRCA1* 185delAG	60-69	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	76 *BRCA1* 185delAG	70-79	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	76 *BRCA1* 185delAG	80+	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	27 *BRCA1* 5382insC	20-29	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	27 *BRCA1* 5382insC	30-39	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	27 *BRCA1* 5382insC	40-49	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	27 *BRCA1* 5382insC	50-59	.	.	.	.

Appendix L. Evidence Table of Penetrance Studies

Author, year	Relative risk breast cancer (95% CI)	General population's risk breast cancer	Ovarian cancer risk *BRCA1* (%, 95% CI)	Ovarian cancer risk *BRCA2* (%, 95% CI)	Ovarian cancer risk *BRCA1* or *BRCA2* (%, 95% CI)	Ovarian cancer risk mutation negative (%, 95% CI)	Relative risk ovarian cancer (95% CI)	General population's risk ovarian cancer
Satagopan et al, 2002	.	.	63 (44-96)	42 (26-73)	.	.	.	.
Satagopan et al, 2002	.	.	1 (0.4-3)	.	.	.	.	.
Satagopan et al, 2002	.	.	3 (1-8)	.	.	.	.	.
Satagopan et al, 2002	.	.	12 (7-25)	.	.	.	.	.
Satagopan et al, 2002	.	.	39 (23-100)	.	.	.	.	.
Satagopan et al, 2002	.	.	66 (37-100)	.	.	.	.	.
Satagopan et al, 2002	.	.	85 (53-100)	.	.	.	.	.
Satagopan et al, 2002	.	.	93 (63-100)	.	.	.	.	.
Satagopan et al, 2002	.	.	1 (0-5)	.	.	.	.	.
Satagopan et al, 2002	.	.	3 (0-14)	.	.	.	.	.
Satagopan et al, 2002	.	.	17 (6-55)	.	.	.	.	.
Satagopan et al, 2002	.	.	22 (11-60)	.	.	.	.	.

Appendix L. Evidence Table of Penetrance Studies

Author, year	Population or risk group	N	Risk to age:	Breast cancer risk *BRCA1* (%, 95% CI)	Breast cancer risk *BRCA2* (%, 95% CI)	Breast cancer risk *BRCA1* or *BRCA2* (%, 95% CI)	Breast cancer risk mutation negative (%, 95% CI)
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	27 *BRCA1* 5382insC	60-69	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	27 *BRCA1* 5382insC	70-79	.	.	.	.
Satagopan et al, 2002	Hospital-based ovarian cancer, Ashkenazi Jewish	27 *BRCA1* 5382insC	80+	.	.	.	.
Struewing et al, 1997[11]	Ad recruitment, Jewish	120 *BRCA1 or BRCA2*	50	.	.	33 (23-44)	4.5 (4.0-5.0)
Struewing et al, 1997	Ad recruitment, Jewish	120 *BRCA1 or BRCA2*	70	.	.	56 (40-73)	13 (12-14)
Struewing et al, 1997	Ad recruitment, Jewish	41 *BRCA1* 185delAG	70	.	.	.	.
Struewing et al, 1997	Ad recruitment, Jewish	20 *BRCA1* 5382insC	70	.	.	.	.
Struewing et al, 1997	Ad recruitment, Jewish	59 *BRCA2* 6174delT	70	.	.	.	.
Warner et al, 199	Breast cancer, prevalent cases Ashkenazi Jewish	34 *BRCA1* + 15 *BRCA2* +	70	59.9	28.3	.	.

Appendix L. Evidence Table of Penetrance Studies

Author, year	Relative risk breast cancer (95% CI)	General population's risk breast cancer	Ovarian cancer risk *BRCA1* (%, 95% CI)	Ovarian cancer risk *BRCA2* (%, 95% CI)	Ovarian cancer risk *BRCA1* or *BRCA2* (%, 95% CI)	Ovarian cancer risk mutation negative (%, 95% CI)	Relative risk ovarian cancer (95% CI)	General population's risk ovarian cancer
Satagopan et al, 2002	.	.	29 (16-69)	.	.	.	.	.
Satagopan et al, 2002	.	.	37 (22-78)	.	.	.	.	.
Satagopan et al, 2002	.	.	44 (29-86)	.	.	.	.	.
Struewing et al, 1997[11]	.	.	.	.	7 (2-14)	0.4 (0.2-0.6)	.	.
Struewing et al, 1997	.	.	.	.	16 (6-28)	1.6 (1.2-2.0)	.	.
Struewing et al, 1997	.	.	12	.	.	.	.	.
Struewing et al, 1997	.	.	22	.	.	.	.	.
Struewing et al, 1997	.	.	.	18	.	.	.	.
Warner et al, 199	.	.	.	.	.	.	.	.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Sub-category	Purpose	Study type	N	Country	Population / Setting
Bish et al, 2002a[155]	Psychological/ Behavioral	To study the effect of inconclusive results of the *BRAC1/2* genes.	Case series	71	England	Women undergoing mutation search testing at Guy's Hospital, London
Bish et al, 2002b[164]	Psychological/ Behavioral	To examine psychological distress before and after genetic cancer counseling with follow-up for women at differing levels of risk: those who have had breast or ovarian cancer, and those who have not, but have low, medium, and high levels of risk	Longitudinal comparative survey study	577	England	Recruited into Department of Clinical Genetics at Guy's Hospital between May 1997 and May 1999

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Inclusion / Exclusion criteria	Family history / Risk level definition	Interventions
Bish et al, 2002a[155]	Inclusion: women with breast or ovarian cancer who had at least a 10% chance of a *BRCA1/2* mutation	Mutation risk level: at least 10% chance of *BRCA1/2* mutation	Women undergoing *BRCA1/2* testing completed questionnaires 2 weeks after blood draws and at 1 week and 6 months after having received a preliminary "inconclusive" result (indicating that 2/3 of the *BRCA1* gene had been tested and no mutation had been found).
Bish et al, 2002b[164]	Inclusion: 1. women already treated for breast or ovarian cancer 2. "affected" and "unaffected" women, classified by risk of developing cancer	4 groups in study: Low risk of developing cancer (< 1 in 6 chance of developing breast or ovarian cancer); Moderate risk (between 1 in 4-6 chance of developing breast or ovarian cancer); High risk (>1 in 3 chance of developing breast or ovarian cancer); Previously had cancer.	Subjects completed a family history sheet detailing the number of cases of cancer in their family, type of cancer, relationship of person to the woman, and age at diagnosis and death. Then they met with a doctor or genetic counselor and completed a more detailed family history using the CASH model to provide a risk estimate (between 45 minutes and 1.5 hours). Basis of genetic inheritance, the implication of genetic testing, and options for screening and surveillance were explained. 4 total questionnaires: pre-consultation, 2 weeks, 6 months, and 12 months post-consultation.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Results
Bish et al, 2002a[155]	Overall: 63 of the 71 women approached to participate in the study chose to do so. Two of these were subsequently found to be carrying a mutation and were excluded from the study. Full data analysis was on 61/71 subjects (86%). Distress levels: During the study period there were no changes in levels of general anxiety (F=0.56)or depression (F=0.38) as measured by HADS. There were no changes in general psychological distress measured by the GHQ-28 (F=0.98). There were no significant changes in level of worry about breast or ovarian cancer (F=2.59 and 0.26). Perception of risk: Perceptions of risk of developing breast cancer decreased during the study, with a significant effect between pre-result and immediately afterward ($p<0.05$). There were no significant changes in screening and surgery intentions.
Bish et al, 2002b[164]	Missing data: Women with incomplete data were younger than those with complete data ($t(418)=2.93$, $p<0.01$), less likely to have a partner ($x2=19.7$, $p<0.001$) or to have children ($x2=3.9$, $p<0.05$). A higher proportion of affected women had incomplete data ($x2=4.6$, $p<0.05$). Description of sample: psychological distress and worry: Significantly less worry about ovarian cancer than breast cancer pre-consultation ($t=15.1(188)$, $p<0.0001$). This difference persisted at 2 weeks ($t=12.8(188)$, $p<0.0001$), 6 months ($t=12.1(188)$, $p<0.0001$), and 12 months ($t=10.0(188)$, $p<0.0001$). Comparison between affected and unaffected women: psychological distress: Greatest reduction in worry occurred between pre-consultation and short term follow-up ($t(186)=7.18$, $p<0.0001$) with a smaller reduction from the 2-week to the 6-month follow-up ($t(186)=2.59$, $p<0.01$). This was sustained until the 12-month follow-up with no significant further decrease ($t(186)=0.82$, ns). A post-hoc test showed that affected women were significantly more worried than women at moderate and high risk about developing ovarian cancer ($p<0.05$). The greatest reduction in perceived likelihood of carrying for perceived likelihood of carrying a genetic mutation for low risk ($F=8.62$, $p<0.001$), moderate risk ($F=4.96$, $p<0.01$), high risk ($F=4.25$, $p<0.01$), and affected women ($F=4.13$, $p<0.01$). Perception of likelihood of carrying a gene mutation was reduced for high risk women following the counseling session ($t(36)=2.95$, $p<0.01$), then significantly increased at 6 months post-consultation ($t(36)=-2.71$, $p<0.01$), and significantly decreased again at 12 months post-consultation ($t(36)=1.87$, $p<0.05$). For affected women, there was a significant reduction in perceived likelihood of carrying a gene mutation at 6 months post-consultation ($t(40)=3.42$, $p<0.01$), followed by a significant increase in perceptions at 12 months post-consultation ($t(40)=-2.48$), $p<0.05$). For low and moderate risk women, other than a significant reduction following counseling for low risk women, perceptions remain stable ($t(23)=2.81$, $p<0.01$).

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Conclusions / Recommendations
Bish et al, 2002a[155]	Giving inconclusive results for *BRCA1/2* testing may be unlikely to cause significant distress.
Bish et al, 2002b[164]	No evidence found that genetic counseling raises worry, in fact, worry about developing breast cancer was reduced following genetic counseling across risk levels. The greatest reduction in worry occurred immediately following genetic counseling, implying a positive effect of counseling. Because this reduction in worry lasted through the 12-month follow-up, this demonstrates long-term positive effectiveness of genetic counseling. Worry was much greater about developing breast cancer than ovarian cancer. The consultation greatly reduced perception of likelihood of carrying the mutation. Groups cannot be separated out for this because there was a significant interaction between time and group for this variable. At 6 months, affected women's perception of likelihood significantly decreased (probably because they received an "inconclusive" result right after the consultation, meaning more testing had to be conducted). Affected women need the same level of counseling as unaffected women and have as many issues and concerns as unaffected women. Actual risk level and perceived risk level were similar and therefore perceptions were realistic.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Sub-category	Purpose	Study type	N	Country	Population / Setting
Brain et al, 2002[156]	Psychological/ Behavioral	To compare the psychological impact of a multidisciplinary specialist genetics service with surgical provision in women at high risk and lower risk of familial breast cancer	RCT	1,000	Wales	Welsh women with family history of breast cancer referred to breast cancer clinic by doctor in 18 month trial period (1996-1997). Randomized to trial (n=366) or control group (n=369).

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Inclusion / Exclusion criteria	Family history / Risk level definition	Interventions
Brain et al, 2002[156]	Exclusion: 1. history of breast cancer 2. prior genetic counseling 3. not a resident of Wales	Family history risk definition: 1st degree female relative diagnosed with breast cancer before age 50; 1st degree female relative with bilateral breast cancer at any age; 2 or more 1st degree relatives with breast cancer; or a 1st and 2nd degree relative with breast cancer. Risk definition: In trial group, risk was assessed on detailed pedigree data collected and analyzed by geneticist using Claus model (Claus et al 1991[105]). In control group, surgical assessment of risk was based on info collected on age, reproductive history, and minimal family history.	Control Group: 1) Breast cancer surveillance, 2) surgical assessment of breast cancer risk, 3) option of entering UK Tamoxifen Prevention Trial, and 4) annual follow-up with surveillance and advice Trial Group: 1, 3, and 4 above AND consultation with a multidisciplinary team with specialist genetic risk assessment and counseling provided by a clinical geneticist and genetic nurse specialist.

Author, year	Results
Brain et al, 2002[156]	Overall: 1,000 persons referred to the trial. 260 not randomized, total of 740 randomized. Control group: 50 lost to follow-up, 2 risk category missing; a total of 315 completed the trial. Trial group: 5 did not receive intervention as allocated, 28 lost to follow-up; a total of 338 completed the trial. State anxiety: Significant main effect of time, with decreased anxiety from baseline to follow-up (p=0.03). Breast cancer worry: Significant overall reduction from baseline to follow-up. Significant interaction between risk information and time. Decline in women at low risk (t(106)=5.92,p<0.001) and moderate risk (t(443)=12.13, p<0.001), but not at high risk. Satisfaction: Significantly lower in high risk group (p<0.001). Perception of risk: Marginally significant trend to increased perceived risk in high risk women in the trial group. Interest in genetic testing: Effect of risk information not significant.

Author, year	Conclusions / Recommendations
Brain et al, 2002[156]	Specialists other than geneticists might provide assessment of breast cancer risk, reassuring those at reduced risk and targeting high risk women for specialist genetic counseling and testing services. Low risk women: Anxiety and cancer concerns were reduced with personal risk information. High levels of satisfaction, whether or not information based on detailed genetic analysis. High risk women: Risk information, even unfavorable, does not appear to create significant anxiety. Concerns about breast cancer risk remained and they were less satisfied with consultation in either group. Implication: breast cancer worry may impact quality of life for women who recognize they are at high risk.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Sub-category	Purpose	Study type	N	Country	Population / Setting
Friedman et al, 1999[157]	Psychological/ Behavioral	To understand the psychological impact of receiving negative *BRCA1* mutation test results in Ashkenazim	Prospective cohort	333	USA	Baylor College of Medicine, Houston, TX

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Inclusion / Exclusion criteria	Family history / Risk level definition	Interventions
Friedman et al, 1999[157]	Inclusion: 1. age 21 or older 2. at least 50% Ashkenazi Jewish ancestry 3. ability to speak-read-write English 4. ability to provide informed consent	Average risk: tested negative and had negative family and personal histories of breast and ovarian cancer. Risk of developing breast or ovarian cancer was that of the general population. Increased risk: tested negative but had positive family or personal histories of breast or ovarian cancer and either had no information about their affected relatives' genetic status or had affected relatives with negative DNA test results. Positive family history defined as one 1st or two 2nd degree relatives with breast cancer (age <50 yrs.) or ovarian cancer.	2-hour educational session including information about frequency of breast and ovarian cancer in general population and in Ashkenazi Jewish population, discovery of the 185delAG mutation, associated risk of breast, ovarian, and colon cancer in women and colon and prostate cancer in men. Also focused on goals of the study, eligibility criteria, possible outcomes of testing and implications for surveillance, recommended screening guidelines in general population, and current surveillance and prevention guidelines for those at increased risk for breast or ovarian cancer. Subjects informed of potential risk of insurance discrimination based on test results. Personal history of cancer obtained by subjects indicating whether they had ever been diagnosed with breast, ovarian, colon, prostate, or other cancer and age of diagnosis. Follow-up questionnaires at 1 and 6 months after notification of test results, then yearly follow-up for 5 years.

Author, year	Results
Friedman et al, 1999[157]	Overall: 333 attended the educational session, 309 consented to study. 289 tested for 185delAG mutation. 6 tested positive and were excluded from the study. Of the 283 remaining, 199 provided complete data on measures used in the study. IES scores: Decreases in cancer-specific distress had occurred in both groups (increased risk and average risk) at the 1-month follow-up. At 6-month follow-up, level of distress in the average risk group had decreased even more, whereas that in the increased risk group had begun a return to baseline. Gender significantly related to IES ($p<0.01$), with women having higher scores. Age was related negatively to IES ($p<0.05$), with younger people scoring higher. Differences between groups: Increased risk and average risk groups differed significantly on the demographic measures (gender and age) entered in the first block ($p=0.003$). Addition of POMS-SF and IES baseline measures in second block did not result in significant change ($p=0.26$); nor was the addition of the same measures at the 1-month follow-up (third block) ($p=0.34$). Addition of the distress measures at the 6-month follow-up (fourth block) also was not associated with significant change ($p=0.07$). With demographic and psychological distress measures at baseline, 1 month, and 6 months, difference between the two groups was statistically significant ($p=0.006$). Standardized regression coefficients for gender (-1.80), age (0.03), and the IES (0.09) differed significantly from zero ($p<0.05$). Although the overall model was significant, difference between groups was based primarily upon differences in IES scores, age, and gender at 6-month follow-up ($p=0.02$, $p=0.03$, and $p=0.02$, respectively).

Author, year	Conclusions / Recommendations
Friedman et al, 1999[157]	After controlling for gender and age, increased risk subjects reported slightly but significantly higher levels of cancer-specific distress than average risk subjects at the 6-month follow-up. For all subjects, general psychological distress declined during this 6 month period. Cancer-specific distress had declined among all subjects at the 1-month follow-up. While the average risk group's cancer-specific distress level continued to decline 6 months after receiving test results, the increased risk group's distress level had begun a climb back to baseline. Data suggest that women and younger people may need more counseling during genetic testing.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Sub-category	Purpose	Study type	N	Country	Population / Setting
Fry et al, 2003[165]	Psychological/ Behavioral	Compare the psychological impact of two models of breast cancer genetic services	Cluster RCT	574	Scotland	From 3/98-11/99, any woman referred from general practice for breast cancer genetic risk counseling. 170 general practices (84% of those invited to participate) were randomized to refer subjects to: 1. standard (regional) service (131/185 subjects completed the trial) or 2. novel (community-based) service (113/188 subjects completed the trial).

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Inclusion / Exclusion criteria	Family history / Risk level definition	Interventions
Fry et al, 2003[165]	Inclusion: 1. resident of region 2. complete baseline questionnaire Exclusion: 1. symptomatic 2. diagnosed with breast or ovarian cancer 3. previous consultation with a different clinic about family history of cancer	Risk of Breast Cancer: Genetics consultant and nurse specialist assigned categorical risk assessment based on Cancer Research Campaign (1977) criteria as follows: Risk of breast cancer is moderately increased if one of the following is present: a) 1st degree relative with a history of breast cancer; b) two 1st or 2nd degree relatives on the same side of the family with breast cancer before age 60 or with ovarian cancer; c) three 1st or 2nd degree relatives on the same side of the family with breast or ovarian cancer; d) 1st degree relative with breast cancer in both breasts; e) 1st degree male relative with breast cancer. If necessary, further information or confirmation of relatives' diagnoses was obtained by a genealogist and from the Scottish Cancer Registry.	Standard (regional) service: Subjects completed a family history form and baseline questionnaire. Those assessed as low risk and their physicians were sent a letter to explain this. Those assessed as moderate or high risk or for whom an adequate risk assessment could not be made were offered an appointment at the familial breast cancer clinic. Clinic consultation involved detailed discussion with genetics consultant and specialist breast surgeon on options for risk management. Clinical breast exam and mammography (where appropriate) were included. After the appointment, subjects' physicians were sent a summary letter. Subjects were asked to participate in a follow-up. Novel (community-based) service: Subjects were sent to an appointment at a community-based clinic run by a genetics nurse specialist who ascertained family history of cancer and compiled a family tree to determine risk assessment. Subjects were informed of risk level by letter. Those at low risk were offered information and reassurance and were discharged from the clinic. They and their physicians were sent a s were asked to take part in a follow-up.

Author, year	Results
Fry et al, 2003[165]	Overall: Of the 574 women invited to participate in the study, 201 were excluded, 23 refused to participate, 123 did not respond, 31 did not return baseline questionnaire (11 for administrative reasons, 13 for protocol violation). 131/185 subjects assigned to the standard service completed the trial (71%); 113/188 assigned to the novel service completed the trial (60%). Cancer worry: For all subjects, there was a significant reduction in scores on the BCWS during the study. Post-hoc analysis revealed the greatest reduction in scores occurred between baseline and 4 weeks ($p<0.0000$) with a smaller significant reduction between 4 weeks and 6 months ($p=0.003$). Distress level: There was a significant decrease in the overall proportion of subjects experiencing "case level " (general psychological) distress over the study period ($p=0.003$), although the reduction was only significant between baseline and 4 weeks ($p=0.0004$).There were no significant differences in the proportion of subjects with "case-level" distress between trial arms or risk groups at 3 different assessment points.

Author, year	Conclusions / Recommendations
Fry et al, 2003[165]	These two models of cancer genetics services evaluated were generally comparable in terms of subjects' psychological outcomes. The proportion of women with "case-level" distress decreased by up to 4 weeks and cancer worry continued to decrease up to 6 months. Unlike in previous studies, reductions in cancer worry were not dependent on objective risk. Decisions regarding implementation of the novel community-based service should be based on the resources required and client satisfaction with the service.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Sub-category	Purpose	Study type	N	Country	Population / Setting
Gilbert et al, 1998[166]	Psychological/ Behavioral	Psychological impact of false-positive mammography and effects of recall on women with and without a family history of breast cancer	Pre-test/Post-test observational	2,357	Scotland	3 health centers in Scotland that were participating in the UKBSP were selected.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Inclusion / Exclusion criteria	Family history / Risk level definition	Interventions
Gilbert et al, 1998[166]	Inclusion: 1. women 2. 50-64 years of age 3. patient of 1 of 3 health centers in Scotland participating in the UKBSP Exclusion: positive for cancer	Familial Risk: Self-reported to radiographer who evaluated risk based on criteria set by the local Department of Medical Genetics. Subjects likely to be at least twice the population risk of breast cancer were considered positive for family history.	Mailed HADS completed before screening. At screening appointment completed HADS (most prior to mammography, a few after mammography). If they were recalled for further testing they completed another HADS and were given two additional HADS to be completed at 5 weeks and 4 months by mail. Health Questionnaire (HQ) completed at screening and recall. Increased risk subjects were informed of this and offered referral for detailed assessment and counseling. If this confirmed increased risk status, they were offered screening every 18 months instead of every 3 years.

Author, year	Results
Gilbert et al, 1998[166]	Overall: Of the 2,357 sent the first HADS, 2,110 (90%) were returned. 1,463 (70%) completed the HADS at screening. 133 were recalled due to increased risk of BC, but 9 were excluded due to cancer diagnosis. 90 subjects completed all HADS. 1,561 (66%) subjects completed the HQ at screening and 105 completed all HQs. On HADS anxiety: Subjects were more anxious at baseline than at the 4-month follow-up (t=2.70, p=0.008), at recall than at screening (t=2.75, p=0.007), and at screening than at the 4-month follow-up (t=2.59, p=0.01). Subjects were less anxious at the 5-week follow-up than at recall (t=3.08, p=0.003), and at the 4-month follow-up than at recall (t=4.13, p<0.0005). On HADS depression: Subjects were more depressed at baseline than at screening (t=2.04, p=0.04), and at recall than at screening (t=2.25, p=0.03). Clinical significance: Subjects were more likely to have borderline or clinically significant anxiety at recall than baseline (p<0.05), screening (p<0.001), 5-week follow-up (p<0.005) or 4-month follow-up (p<0.02). Overall distress levels returned to normal within 5 weeks. Effects of positive family history: Subjects with a family history of breast cancer were more anxious than those without at the 4-month follow-up (F=4.14, p=0.045). Subjects with a family history of breast cancer were less likely to have borderline or clinically significant depression than those without a family history of breast cancer (X2=5.76, p<0.02). Subjects with a family history of breast cancer were less likely to have stress-related changes on the HQ at screening than those without a family history of breast cancer (F=6.38, p=0.01). Subjects without a family history of breast cancer were more anxious at baseline than at the 4-month follow-up (F=4.57, p=0.05). There was no significant difference between the two groups in proportions of subjects with borderline or significant anxiety. Subjects with incomplete data: Subjects who did not return the 5-week follow-up HADS were more depressed at screening and baseline (t=2.46, p=0.02 and t=2.61, p=0.01 respectively). Ss who did not return the 4-month follow-up HADS were more depressed at screening and baseline (t=2.26, p=0.03 and t=1.96, p=0.05 respectively).

Author, year	Conclusions / Recommendations
Gilbert et al, 1998[166]	Women were more likely to have significant anxiety at recall visits than screening, but the anxiety was transient and significantly lowered after 5 weeks. Contrary to the hypothesis, women with a family history were less likely to be significantly depressed at screening. This implies that screening may be reassuring to these women. Recalling women with family history to assessment clinics only causes increased anxiety. Sending them their results with the option to attend genetic clinics could help alleviate this anxiety.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Sub-category	Purpose	Study type	N	Country	Population / Setting
Hopwood et al, 1998[158]	Psychological/ Behavioral	To understand psychological support needs for women at high genetic risk for breast cancer	Cohort	176	England	All were consecutive first-time attendees at the Family History Clinics (Manchester, UK).
Lerman et al, 1998[159]	Psychological/ Behavioral	To identify members of hereditary breast and ovarian cancer families who are at risk for adverse psychological effects of genetic testing	Prospective cohort	396	USA	Men and women who were members of 33 extended hereditary breast or ovarian cancer families in a hereditary cancer registry (27 *BRCA1* -linked and 6 *BRCA2* linked). Study enrollment: 7/94-2/97.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Inclusion / Exclusion criteria	Family history / Risk level definition	Interventions
Hopwood et al, 1998[158]	Inclusion: 1. women aged 18-45, 2. living within a 25-mile radius of the FHC	Risk was at least twofold greater than the population for breast cancer (i.e., 1:6 lifetime risk or greater as assessed using the Claus model).	Women were interviewed 3 months after genetic risk counseling because of a family history of breast cancer. 1. Postal questionnaire prior to counseling. 2. At attendance for risk counseling, women were asked to complete GHQ together with several other self-report measures. 3. Questionnaires completed again at 3, 6, 9, and 12 months later. 4. Home visit conducted at 3 months to carry out research interviews, which included administration of the Psychiatric Assessment Schedule.
Lerman et al, 1998[159]	Inclusion: 1. 18 or over 2. unaffected at-risk family members (without cancer) and those with cancer Exclusion: people with psychiatric or cognitive disorders	Not reported	Structured baseline phone interview. Family information session on *BRCA* testing, 1-2 hours duration, with semi-structured protocol including field trips. Option of phone education session instead. All were given option of receiving *BRCA1/2* test results. Those who received results participated in an individual counseling session with an oncologist, including information on personal cancer risk for self and offspring, and available options for surveillance and prevention. At 1 and 6 months post-disclosure, all subjects were re-contacted by phone to assess psychological distress.

Author, year	Results
Hopwood et al, 1998[158]	Overall: Of 176 women approached, 174 agreed to participate in the study, but 7 declined the interview, 7 were lost to follow-up, and 2 were subsequently found to be ineligible. GHQ scores: Compliance at baseline was 85% (n=34), and 94% at 3 months (n=148). Prevalence of psychological distress, with a cut-off score >5, was 30.6% at baseline and 26.4% at 3 months. An examination of the 4 subscales of GHQ showed that 9.7% scored ≥5 on the somatic scale, 14.2% on the anxiety subscale and 3% each on the depression and suicidal ideation subscales at baseline. At 3 months, proportions were 12.2%, 14.9%, 6.8%, and 3.4%, respectively. When analysis was restricted to 105 women with evaluable assessments on all occasions, prevalence was 30.5% and 24.8% respectively. Baseline scores compared with pre-counseling risk estimates showed no significant difference (p=0.087). Significant difference between psychological distress and perceived risk post-counseling (p=0.0053). Women with accurate risk knowledge post-counseling had significantly lower scores than those who underestimated (p=0.0034) or who overestimated (p=0.0447). Psychiatric Assessment Schedule: Psychiatric disorder was confirmed in 21 (13.3%) of the study participants at 3 months. Most women had multiple concerns, but none reported risk counseling as a precipitant for their distress. Estimation of risk: Previous to risk counseling, 10% accurately estimated risk of breast cancer, while 50% accurately estimated after (p=0.0000). More women continued to overestimate (17%) than underestimate (11%). In general, giving women an accurate estimate of their probability of breast cancer when they perceived it to be much lower did not appear to trigger clinical anxiety or depression.
Lerman et al, 1998[159]	Overall: 396 individuals completed a baseline interview. Retention rate was significantly higher for women (86%) than men (76%) (p=0.008), and for mutation carriers and non-carriers (91%) compared with those who declined to receive results (p=0.001). Of the 327 subjects, 109 were non-carriers, 97 were mutation carriers and 121 declined to receive test results. Distress levels: Presence of cancer-related stress symptoms at baseline was strongly predictive of the onset of depressive symptoms in family members who were offered but declined testing. At follow-up evaluation, 8% of noncarriers, 14% of carriers, and 19% of decliners were depressed (p=0.02). At the 1-month follow-up interview, there was a significant association between study group and depression in the high-stress subgroup (p=0.001). At 1 month, depression rates increased from 26% to 47% in subjects with high levels of baseline distress who declined test results, while rates in non-carriers decreased from 41% to 11% (p=0.0004). There was no change in depression rates in mutation carriers (20% to 23%). These significant differences were evident at the 6-month follow-up (p=0.04).

Author, year	Conclusions / Recommendations
Hopwood et al, 1998[158]	Prevalence rate for psychological distress when measured by a self-report questionnaire was double that ascertained by psychiatric interview, which is regarded as the gold standard. Other studies using self-report measures should interpret data with this in mind. Interview data suggests that psychiatric morbidity was not apparently caused by the genetic counseling. This suggests that routine genetic risk consultations do not facilitate disclosure of distress or unresolved grief, and the use of a screening instrument together with a second-stage assessment interview should be explored further.
Lerman et al, 1998[159]	In *BRCA1/2*-linked families, persons with high levels of cancer-related stress who decline genetic testing may be at risk for depression. They may benefit from education and counseling and should be monitored for possible adverse effects.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Sub-category	Purpose	Study type	N	Country	Population / Setting
Lobb et al, 2004 [160]	Psychological/ Behavioral	To examine the effect of different consultant communication styles on a variety of outcomes	Longitudinal	193	Australia	Women from high-risk breast cancer families attending their first consultation before genetic testing
Lodder et al, 2001 [168]	Psychological/ Behavioral	To identify individuals at risk for high distress in the weeks following disclosure of *BRCA 1/2* mutation test result	Pre-test/Post-test observational	118	Netherlands	University Hospital, Rotterdam; subjects part of an evaluation of distress in healthy women who apply for genetic testing with their partners

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Inclusion / Exclusion criteria	Family history / Risk level definition	Interventions
Lobb et al, 2004 [160]	Inclusion: 1. 18 or over 2. able to give written consent 3. fluent in English 4. no prior testing for or carrier of *BRCA1* or *BRCA2*	Not reported	Self-administered questionnaires were mailed when the appointment was made and 4 weeks after their genetic consultation. Questionnaires included Breast Cancer Genetics Knowledge, Expectations, Perceived Risk, IES, HADS, and Satisfaction with Genetic Counseling Scale. Women came to the center for their genetic consultation. The consultation was recorded, analyzed, and coded to capture 10 aspects of genetic counseling. Not all counselors incorporated all aspects and this was the basis for the study.
Lodder et al, 2001 [168]	Inclusion: 1. healthy women with a 25% or 50% risk of being a *BRCA1/2* carrier 2. applied for *BRCA1* genetic testing at the University of Rotterdam between 12/95-4/98. 3. subjects asked their partners to participate	Genetic risk: subjects have a 25% or 50% risk of being a *BRCA1/2* carrier.	Pre-test assessment prior to blood sampling, with subjects taking home questionnaires to complete. Pre-test interview usually scheduled in the weeks following blood sampling, but 14% occurred just after the genetic counseling session. After disclosure of test result, psychologist met with subjects and their partners to discuss feelings. Post-test assessment (questionnaires and interviews) occurred 1 -3 weeks later. 58% of interviews occurred in subjects' homes, 35% in the hospital clinic, and 7% by phone, all according to subject's preference.

Author, year	Results
Lobb et al, 2004 [160]	Anxiety: Women who had more aspects of genetic testing discussed had a decrease in anxiety after 4 weeks (p=0.03). Women receiving a letter summarizing their consultation had lower anxiety (p=0.012) and a trend toward less anxiety about breast cancer (p=0.089). Women who received four or more supportive communications were more anxious about breast cancer (p=0.000). Depression: Women whose consultants facilitated understanding more had a decrease in depression (p=0.052). Risk Accuracy: Women receiving a letter summarizing their consultation had increased risk accuracy (p=0.023).
Lodder et al, 2001 [168]	Overall: 118 women and their partners were asked to participate; 21% decided not to and 9% dropped out, leaving 78/118 (66%) and 56 partners. Distress levels: The course of anxiety and depression from pre-test to post-test was significantly different for *BRCA* and non-*BRCA* subjects (p<0.05). Non-*BRCA* subjects became less anxious and depressed from pre- to post-test, and BRCA subjects showed a slight increase in anxiety and depression. Level of post-test anxiety, depression, and cancer-related distress was strongly related to the level of pre-test distress on the same scales (p varies from 0.0001 to 0.05). Non-*BRCA* subjects who recently had a sister identified with *BRCA* had higher post-test levels of depression than other non-*BRCA* subjects and *BRCA* subjects (p=0.01). Partners of *BRCA* subjects reported higher distress levels at post-test than non-*BRCA* partners, and 1/3 had borderline to high anxiety levels at post-test. Level of cancer-related distress in partners of *BRCA* subjects was low.

Author, year	Conclusions / Recommendations
Lobb et al, 2004 [160]	Women who understand what is being presented to them have decreased depression. This can imply that women may feel overwhelmed with the amount of information they receive and may feel worse if they are not helped to understand it. Providing a written summary of the consultation helped with accurate risk perception.
Lodder et al, 2001 [168]	*BRCA* mutation carriers who are anxious at pre-test would likely benefit from assessment for psychological support, as would non-mutation carriers with a sister who received a positive *BRCA* test result.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Sub-category	Purpose	Study type	N	Country	Population / Setting
Lodder et al, 2002[167]	Psychological/ Behavioral	To understand the emotional impact of genetic testing outcome and decisions on risk management	Pre-test/Post-test observational	118	Netherlands	118 women who underwent genetic testing at the University Hospital, Rotterdam between 12/95-04/98 were asked to participate with their partners.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Inclusion / Exclusion criteria	Family history / Risk level definition	Interventions
Lodder et al, 2002[167]	Inclusion: 1. 50% risk of carrying *BRCA1/BRCA2* mutation 2. healthy 3. women Exclusion: 25% risk of carrying *BRCA1/BRCA2* mutation	50% risk of being a *BRCA1/2* mutation carrier.	Subjects came in for genetic counseling and testing. If found to have a mutation in *BRCA1/2* they were referred to the Family Cancer Clinic of the Daniel den Hoed Cancer Center/University Hospital, Rotterdam to discuss the implications. Subjects then decided on their plan of action (either prophylactic mastectomy or surveillance). Subjects were asked to participate in the psychological study at testing time. Right after meeting with genetic counseling the subjects met with a psychologist and were given the questionnaires to complete. Directly after test disclosure subjects met with the psychologist again. There were follow-ups at 1-3 weeks and 6 and 12 months after test disclosure. Subjects were split into 3 groups: 1) undergoing prophylactic mastectomy (average age 35, n=14), 2) undergoing surveillance (average age 42, n=12), and 3) non-mutation carriers (average age 37, n=37).

Author, year	Results
Lodder et al, 2002[167]	Overall: Of the 118 asked to participate, 93 signed the informed consent (78%). 11 dropped out prior to the second assessment and 3 dropped out during the follow-up phase, leaving 79, but 16 were excluded because they only had 25% risk. 63 were left (26 mutation carriers and 37 non-mutation carriers) (53% response rate). 12 did not complete all questionnaires. Distress: Mutation carriers undergoing prophylactic mastectomy had higher anxiety at all points than the other two groups ($p<0.05$). Mutation carriers undergoing surveillance had lower anxiety than the other two groups, except at post-test. Non-mutation carriers were similar to mutation carriers undergoing surveillance on their level of distress for post-test and follow-up. Non-mutation carriers were more distressed and anxious pre-test than post-test and follow-up. There were more mutation carriers undergoing prophylactic mastectomy with borderline to high anxiety (29%) at 1-year follow-up than for the surveillance group (8%) or the non-mutation carriers (16%). 3 subjects who opted for prophylactic mastectomy and 2 non-mutation carriers requested psychological support within 12 months following the results, no one in the surveillance group di levels similar to those of the normal female population prior to the results. All levels of anxiety were similar to or lower than the normal female population at 12-month follow-up. Body Image: Only 11 of those who opted for prophylactic mastectomy, 8 who opted for surveillance, and 18 non-mutation carriers completed these questionnaires, due to deciding not to and administrative issues. 8 partners of subjects who opted for prophylactic mastectomy and 13 partners of subjects in either the surveillance group or non-mutation carriers completed their questionnaires. Subjects in the prophylactic mastectomy group were similar to the surveillance group on importance of their physical appearance and their sexual relationship at pre-test ($p=0.17$ and $p=0.6$, respectively). At pre-test subjects in the prophylactic mastectomy group reported more problems than the other groups. The prophylactic mastectomy group reported more body image/sexuality problems post-test. Non-mutation carriers' body image/sexuality increased at post-test.

Author, year	Conclusions / Recommendations
Lodder et al, 2002[167]	The majority of women undergoing prophylactic mastectomy were between 30-40 years of age and had young children. Only one women was between 30-40 years of age, and one had young children in the surveillance group. Women undergoing prophylactic mastectomy had higher levels of distress over the study period, many of whom had made the decision pre-test. The low anxiety in the surveillance group might be linked to their trust of the surveillance process. Women in the prophylactic mastectomy group were less satisfied with their body image/sexuality pre-test. The majority of women in the prophylactic mastectomy group did not regret their decision, but this could be related to "cognitive dissonance."

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Sub-category	Purpose	Study type	N	Country	Population / Setting
Meiser et al, 2001[169]	Psychological/ Behavioral	To evaluate the impact of genetic counseling in women at risk of developing hereditary breast cancer	Comparative	276	Australia	14 familial cancer clinics and 6 outreach clinics in 5 Australian states (New South Wales, Victoria, South Australia, Queensland, and Western Australia). Clinics provide comprehensive service including risk assessment, genetic testing, and advice on early detection and prophylactic strategies.
Meiser et al, 2002[161]	Psychological/ Behavioral	To study the psychological adjustment of women who have undergone testing for *BRCA 1/2* breast and ovarian cancer susceptibility	Prospective cohort	143	Australia	Between 11/96 and 10/00, women in outreach clinics (30 *BRCA* carriers, 60 non-carriers) who had *BRCA1/2* testing and 53 women not tested (control group). Subjects were healthy with a family history of breast or ovarian cancer who approached 1 of 14 familial cancer clinics (FCC) and 6 associated clinics.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Inclusion / Exclusion criteria	Family history / Risk level definition	Interventions
Meiser et al, 2001[169]	Inclusion: unaffected women with a family history of breast cancer Exclusion: 1. prior diagnosis of breast or ovarian cancer 2. unable to give informed consent 3. limited literacy in English 4. received a genetic test result prior to attending for genetic counseling or during the follow-up period	Clinic staff were asked to make a judgment on whether a subject's family history was either consistent or not consistent with a dominantly inherited predisposition to breast cancer. Subjects were then classified as being at high risk or moderately increased risk. Moderately increased risk: lifetime risk of 1 in 4 to 1 in 8. High risk: lifetime risk of 1 in 2 to 1 in 4. Pedigrees and relative's medical records were confirmed to support risk level judgment. Expert opinions of clinical geneticists were used as a gold standard to estimate breast cancer risk in high-risk women (since no universally accepted standards exist).	Baseline questionnaires 12-month follow-up questionnaires
Meiser et al, 2002[161]	Inclusion: 1. no history of breast or ovarian cancer 2. eligible for genetic testing 3. at risk for developing hereditary breast cancer with an affected living relative to provide blood sample Exclusion: 1. limited English literacy 2. being tested for founder mutations only	Used for estimate of risk, pre-genetic testing. 25% mutation (*BRCA1/2*) carrier risk: Subjects from high risk family with closest affected relative or relative with a *BRCA* mutation is 2nd degree. 50% risk: Subjects from high risk family who has either a 1st degree affected relative or unaffected relative with a known pathogenic *BRCA1/2* mutation.	Comprehensive service provided to all including risk assessment, genetic testing, and advice regarding cancer surveillance and prophylactic strategies. Subjects invited to participate via pre-clinic phone call before face-to-face genetic counseling. Questionnaires and consent forms were mailed and subjects returned them prior to their appointment. Follow-up questionnaires were mailed at 7-10 days, 4 months, and 12 months post-disclosure for subjects receiving test results. Each time a subject received a test result, an analogous mail-out of follow-up questionnaires was triggered to a recently recruited control subject when one was available. Subjects not eligible for testing because of no living relative from whom a blood sample could be obtained served as controls. Reminder calls were made as required.

Author, year	Results
Meiser et al, 2001[169]	Overall: Of 276 eligible women, 30 declined or did not return baseline questionnaire (89% response rate). Of these, 218 returned the 12-month follow-up questionnaire (79% response rate), comprising the final sample. Breast cancer knowledge: Scores of breast cancer knowledge increased significantly from baseline to follow-up ($p<0.0001$). Breast cancer genetics knowledge at baseline ($p<0.0001$) and educational level ($p=0.025$) were significantly associated with breast cancer genetics knowledge at follow-up. No other variables were significantly correlated. Perception of risk: No overall association between educational level and changes in magnitude of perceived risk from baseline to follow-up ($p=0.347$). Overall proportion of women whose risk perception accuracy improved, compared with those whose perception deteriorated, was not significant ($p=0.36$). A logistic regression predicting improvement in accuracy of perceived risk at 12-month follow-up showed that neither age ($p=0.55$), objective risk ($p=0.99$), marital status ($p=0.53$), nor educational level ($p=0.17$) were significantly associated. Anxiety levels: At baseline, BDI mean = 6.2, STAI-state mean = 35.8, IES mean = 15.1. At 12-month follow-up, BDI mean = 7.4, STAI-state mean = 37.3, IES mean = 13.8. Inspection of means did not suggest differences from baseline to 12-month follow-up for BDI and STAI-state. There was a statistically significant decrease in breast cancer anxiety from baseline to follow-up ($p=0.037$), which was significantly associated with improvements in perceived risk ($p=0.008$). None of the other sociodemographic and family history variables were associated with changes in breast cancer anxiety at follow-up.
Meiser et al, 2002[161]	Overall: 89% of eligible subjects returned baseline questionnaire; overall follow-up rate was 80%. Comparison: Compared with controls, *BRCA* subjects had significantly higher breast cancer distress post-notification: 7-10 days ($p=0.005$) and 12 months ($p=0.045$). Trend: higher breast cancer distress 4 months post-notification ($p=0.054$). Compared with controls, *BRCA* subjects showed significant decrease in state anxiety 12 months post-notification ($p=0.0007$), and *BRCA* negative subjects showed a significant decrease in state anxiety 7-10 days post-notification ($p=0.024$). *BRCA*- negative subjects showed a trend of lower state anxiety than controls at 4 months post-notification ($p=0.066$). *BRCA*- negative subjects had a decrease in depression at 4 months post-notification ($p=0.024$) compared with controls.

Author, year	Conclusions / Recommendations
Meiser et al, 2001[169]	Breast cancer genetics knowledge was significantly improved 12-months post-counseling. Greater increases in knowledge were associated with higher education levels. Statistically significant decrease in breast cancer anxiety 12-months post-counseling. Improvements in perceived risk were associated with decreases in breast cancer anxiety at the 12-month follow-up, suggesting that the anxiety-reducing effects of genetic counseling may be the result of more accurate risk perceptions. It is unknown what mechanisms account for the association between improvements in perceived risk and reductions in breast cancer anxiety. It is plausible that women feel reassured by lower than expected risk estimates leading to decrease in breast cancer anxiety. Future studies should explore whether providers of genetic counseling present information on advantages and disadvantages of screening strategies in different ways, depending on a woman's educational level. Content of genetic counseling should be reviewed to ensure women receive and take away the right message.
Meiser et al, 2002[161]	Those without deleterious *BRCA* mutations derive psychological benefits from genetic testing. Those who test positive for deleterious *BRCA* mutations may anticipate a sustained increase in breast cancer distress following disclosure, although no other adverse effects were found in this group

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Author, year	Sub-category	Purpose	Study type	N	Country	Population / Setting
Ritvo et al, 2000[170]	Psychological/ Behavioral	To report on the psychological responses of women given familial-genetic evaluations for ovarian cancer risk	Pre-test/Post-test observational	78	Canada	Between 10/97 and 7/98, women in Toronto, self- or doctor-referred due to suspected genetic ovarian cancer risk to Familial Ovarian Cancer Genetic Clinic (FOCGC). Cohort A: Eligible subjects consisted of 78 women who attended FOCGC for initial appointments and familial genetic risk assessment.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Inclusion / Exclusion criteria	Family history / Risk level definition	Interventions
Ritvo et al, 2000[170]	Inclusion: suspected genetic ovarian cancer risk	High risk: 1) 2 or more 1st degree relatives with breast or ovarian cancer < age 50, 1 of whom had ovarian cancer; or 2 or more affected relatives who are descendants of an ethnic group with known high *BRCA* mutation, 2) or 4 2nd or 3rd degree relatives diagnosed with breast or ovarian cancer < age 50, 3) or family pedigree consistent with autosomal dominant pattern of inheritance. Moderate risk: 1) At least one 1st degree relative with breast or ovarian cancer before age 50; additional 2nd or 3rd degree relatives meeting the same criteria that increase risk substantially, 2) or one 1st degree relative meeting the same criteria who is a descendant of an ethnic group with known high *BRCA* mutation incidence. Low risk: 1) a 1st degree relative with ovarian cancer or one with breast cancer before age 50, 2) 2nd or 3rd degree relatives with ovarian cancer and/or breast cancer who do not meet criteria as above for moderate or high risk.	Family history questionnaire and baseline psychiatric battery sent to subjects for completion prior to first clinic appointment. Those with eligible family history given appointment for complete family genetic assessment. Standard method used to orient subjects and to obtain information. Initial visit: subject seen by team of genetic counselor, geneticist, and gynecologist oncologist. Family history/pedigree reviewed and subject assigned to low, moderate, or high risk category. Baseline questionnaire. Initial and follow-up appointments: pelvic exam, transvaginal ultrasound, and serum CA-125 screening. All questionnaires completed at home or in clinic with assistance of research assistant as needed. Immediately after clinic assessment, subjects completed brief survey, and a semi-structured phone interview occurred 48-72 hours later. Follow-up assessment by mail 9 and 12 months later.

Author, year	Results
Ritvo et al, 2000[170]	Overall: 23% drop-out rate between baseline and follow-up. Drop-outs were younger (p=0.07) and scored lower on the optimism test (p<0.02) than subjects. Depression levels: Higher self-assessed cancer risk levels (vs. as assessed by professionals) at baseline predicted higher level of depression at follow-up (p<0.03). This was especially visible in the high risk group: 57% of subjects who reported self-assessment of high risk were depressed, while only 15% of subjects categorized by professionals as high risk were depressed. Optimistic expectancy was a significant factor in depression score variance. Subjects who were more optimistic at baseline were less likely to be distressed or depressed at follow-up 9 or 12 months later (p<0.001) Although the study refers to 2 longitudinal cohorts, no statistically significant data are presented on Cohort B.

Author, year	Conclusions / Recommendations
Ritvo et al, 2000[170]	Assisting people in understanding their risk status and adapting to risk assessment is a fundamental part of the counseling process.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Sub-category	Purpose	Study type	N	Country	Population / Setting
Smith et al, 1999[162]	Psychological/ Behavioral	To determine the effect of siblings' test results on psychological distress 1-2 weeks after *BRCA1* mutation testing	Longitudinal	500	USA	Genetic counseling sessions took place at University of Utah. Most kindred members live in Utah and Idaho and are Mormon.
Warner et al, 2003[171]	Psychological/ Behavioral	To asses the usefulness of an information aid on women's knowledge, breast cancer related anxiety, risk perception, and attitudes toward screening and to evaluate women's satisfaction with the aid.	Pre-test/Post-test	203	Canada	Family practices in Ontario where the physicians are members of the College of Family Physicians of Canada's National Research System. Recruitment took place between February 1999 to May 2000.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Inclusion / Exclusion criteria	Family history / Risk level definition	Interventions
Smith et al, 1999[162]	Inclusion: age 18 or older Exclusion: 1. unable to consent 2. unable to attend two in-person genetic counseling sessions	All subjects are members of Kindred 2082 (K2082), the largest known kindred identified with a *BRCA1* mutation. More than 750 living adult members have been identified. Most kindred members live in Utah and Idaho and are Mormon.	Subjects given baseline questionnaire. Subjects who still wished to be tested received extensive pre- and post-test family and genetic counseling with a genetic as well as a marriage and family counselor. After the first session, subjects had blood drawn for DNA analysis. Results were provided at second session, if subjects elected to receive results. 1-2 weeks later, subjects were contacted for the first follow-up interview. Additional questionnaires were administered at various points in time up to 2 years after receiving results (these data are not used in this paper).
Warner et al, 2003[171]	Inclusion: 1. English speaking 2. female 3. patient of physician from the College of Family Physicians of Canada's National Research System 4. older than 18 years 5. any family history of breast cancer	Low risk Moderate risk High r+J17isk (specified, but not defined in article)	A baseline questionnaire was completed in the doctor's office. Then subjects given an "information aid" consisting of a booklet (at 8th grade reading level) and a 30-minute audiotape that together highlight breast cancer pathogenesis, risk factors, prevention, screening, and presentation; an overview of breast cancer genetics; and criteria to help women identify their risk level themselves. Three case scenarios of women at low, moderate, and high risk of breast cancer are presented in the materials. A second questionnaire was completed at home. A third questionnaire was mailed 4 weeks after the second.

Author, year	Results
Smith et al, 1999[162]	Overall: Of 500 eligible subjects, 82% (n=408) completed the baseline interview, 59% (n=296) also completed first counseling session, and 54% (n=269) had blood drawn for purposes of mutation testing. 91% (269 of 296) who received counseling decided to be tested. Of 269 who completed baseline and had blood drawn, 88% (n=238) received test results in person from a genetic counselor, and 86% (n=230) completed the follow-up interview 1-2 weeks after receiving results. Of these 230, 92% (n=212) were tested, received results, completed the 1-2 week follow-up, and had complete data on all relevant variables. IES scores: At the 1-2 week interview, there was high level of consistency with Cronbach's α of 0.88 (0.89 for females and 0.84 for males). The Intrusion and Avoidance subscales have a simple Pearson correlation coefficient of 0.64 ($p<0.01$). Interaction Effects Model: For women, the adverse effect of being a carrier vs a noncarrier on test-related distress was significant. The undesirable effects of testing positive were attenuated when tested siblings were all positive ($p<0.10$) and when siblings had mixed results ($p<0.01$). These findings strongly suggest that the largest adverse consequences for carrier women were among those whose tested siblings were noncarriers. Summary: Largest adverse psychological consequences for female carriers, relative to noncarriers, were for those who were tested first and those whose tested siblings were noncarriers. Results suggest that individuals' immediate reaction to test results varies by the results of their siblings, although this association varies by gender.
Warner et al, 2003[171]	Overall: Of 405 randomly selected physicians, 97 agreed to recruit up to 6 (median=3) subjects. 59 of these physicians enrolled (61%). 203 were recruited, and 160 completed all three questionnaires (79%). 39% low risk, 35% moderate risk, 26% high risk. The information aid was rated excellent or very good by 91% of the women; 96% thought it should be available in family physicians' offices. Satisfaction with information: There were significant differences in satisfaction with the information aid by hereditary breast cancer risk level. Those at low risk rated increased knowledge of hereditary breast cancer 97%, whereas those at high risk rated knowledge 72% ($p<0.001$). Those at low risk rated increased understanding of hereditary breast cancer 95%, whereas those at high risk rated increased understanding 81% ($p<.034$). Those at low risk rated how well it answered questions about hereditary breast cancer 92%, whereas those at high risk rated this 77% ($p<.051$). Knowledge of breast cancer: Knowledge of genetics, incidence, and disease prevention and treatment improved significantly overall with 3 out of 11 items ($p<0.0001$), 2 out of 11 items ($p=0.001$), and 5 out of 11 items ($p=0.027$), although Breast cancer worry: Worry about breast cancer did not differ at baseline across the 3 risk groups and was not affected by u the aid. There was a significant increase from 85% to 96% ($p<0.001$) in intent to undergo clinical breast examination, particularly in the low and moderate risk groups.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Conclusions / Recommendations
Smith et al, 1999[162]	Studies of high risk families provide an opportunity to preview how genetic testing results may affect individuals within a family context. The familial context in which genetic counseling is conducted may be important for understanding how individuals react to their own test results. Future investigators should anticipate how psychological consequences and family dynamics may change when genetic testing is conducted in other settings, where individuals do not have access to such counseling services. This study is the first to report the short-term psychological effects of *BRCA1* testing among tested family members.
Warner et al, 2003[171]	The information aid is a useful resource for women and primary care physicians and could facilitate appropriate risk assessment and management of women with a family history of breast cancer.

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Sub-category	Purpose	Study type	N	Country	Population / Setting
Watson et al, 1999[163]	Psychological/ Behavioral	To investigate perception of genetic risk and the psychological effects of genetic counseling in women with a family history of breast cancer	Prospective cohort	303	England	First-time genetic clinic attendees recruited from four South London genetic counseling centers (Royal Marsden NHS Trust Hospital [two separate clinics], Mayday University Hospital, and St. Georges' Hospital)

Appendix M. Evidence Table of Studies of Adverse Effects of Risk Assessment and Testing

Author, year	Inclusion / Exclusion criteria	Family history / Risk level definition	Interventions
Watson et al, 1999[163]	Inclusion: 1. female with family history of breast cancer 2. never clinically affected by cancer 3. no known serious mental illness 4. age 18 or older 5. able to complete a questionnaire	Breast cancer risk calculated using CASH model based on the number of breast cancer cases in 1st and 2nd degree relatives, age of family members at disease onset, and age of woman presenting for genetic counseling.	Self-administered questionnaires given at genetic clinic immediately, pre- and post-genetic consultation and by postal survey at 1-, 6-, and 12-month follow-ups.

Author, year	Results
Watson et al, 1999[163]	Overall: Of the 303 eligible, 10 were not approached due to clinic time constraints, another 10 declined invitation, and 1 was excluded for missing baseline data, comprising final sample of 282. No significant difference on demographic variables from non-participants. Response rate was 96% (n=272) immediately post-counseling, 88% (n=249) at 1- and 6-month follow-ups, and 93% (n=263) at 12 months. GHQ: One-third had notable levels of distress. There was no statistically significant change in general mental health at each follow-up compared with pre-counseling level. Cancer Anxiety and Helplessness / IES: No statistically significant changes in levels of cancer-specific distress. Follow-up assessment revealed that 13% (35/268) had received some psychological intervention during the 12 months since attending the clinic. Of these, 7% (n=19) had received psychotropic medication, 4% (n=10) had engaged in psychological counseling, and 2% (n=6) had received both forms of intervention. Levels of state anxiety: Anxiety levels at pre-counseling were at similar levels to those reported in healthy women attending for breast cancer screening (mean 38.7), with a significant downward shift immediately post-counseling (mean 35.2, p<0.00 Perception of risk: Specific figures about risk, provided within genetic counseling, tend not to be remembered. Continual over-estimators may be worrying unnecessarily and excessively about breast cancer risk and under-estimators appear undisturbed by the information that their risk is greater than they thought. Under-estimators were not significantly different from the rest of the sample in terms of their scores for intrusive and avoidant thoughts about breast cancer risk when assessed pre-counseling. However, at 12 months, their scores were significantly lower than the rest on each of the scales (avoidance p=0.02; intrusion p=0.006), indicating that in the long-term they are less likely to report having intrusive thoughts about breast cancer risk. High levels of cancer-specific distress were found in pre-genetic counseling, with 28% reporting that they worried about breast cancer "frequently or constantly" and 18% that worry about breast cancer as a "severe or definite" problem. Following genetic counseling, levels of cancer-specific distress were unchanged. General mental health remained unchanged over time (33% psychiatric cases were detected pre-genetic counseling, and 27% 12 months after genetic counseling).

Author, year	Conclusions / Recommendations
Watson et al, 1999[163]	Evidence indicates that there are high levels of cancer-related worry that compare unfavorably to previously gathered data on general population risk samples. The finding that genetic counseling fails to alleviate this cancer-specific distress in a substantial minority of women is contrary to previous US findings, reporting a reduction in cancer anxiety several months post-counseling. However, a single counseling session may not be sufficient to shift worries in some women and probably unreasonable to expect otherwise. General levels of psychological morbidity remain unaffected by genetic counseling. Of concern is the substantial minority of women who did not benefit from counseling because they continued to overestimate risk and their worry about developing breast cancer was unrelieved. Also, a small group of women who underestimated risk may have failed to benefit in terms of future management of their health because they continued to underestimate risk following counseling. Summary: This study highlights some problems in the provision of cancer genetic counseling. Some women continue to believe they are at high risk despite being told otherwise. Anxiety about breast cancer is not alleviated by genetic counsel

BCWS, Breast Cancer Worry Scale; BDI, Beck Depression Inventory; BSI, Brief Symptom Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; GHQ, General Health Questionnaire (12-, 28-, or 30-item); GSI, Global Severity Index; HADS, Hospital Anxiety and Depression Scale; IES, Impact of Events Scale; NSI, non-standardized instrument; POMS-SF, Profile of Mood States short form; RCT, randomized controlled trial; SCL-90, Symptom Checklist--90; STAI, State-Trait Anxiety Inventory; UKBSP, UK Breast Screening Programme.

Appendix N. Quality Ratings of Studies of Adverse Effects of Risk Assessment and Testing Studies

Author, year	Study design	Random assignment?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Blinding: outcome assessors, care provider, patient?	Clear definition of measures?	Intention-to-treat analysis?
Bish et al, 2002a[155]	Case series	No	N/A	N/A	Yes	N/A	Yes	N/A
Bish et al, 2002b[164]	Prospective cohort	No	N/A	Insufficient data to determine	Broad criteria specified	N/A	Yes	No
Brain et al, 2002[156]	RCT	Yes	Concealed in baseline questionnaire and in clinic appointment letter	Yes	Yes	Implied: individual randomization to trial or control clinic by computer-generated sequence	Yes	Yes
Friedman et al, 1999[157]	Prospective cohort	No	N/A	Demographic differences reflect those typical of the different risk groups	Yes	N/A	Yes	N/A
Fry et al, 2003[165]	Group RCT	Yes	Not reported	No	Yes	Not reported	Some measures not standard One not clearly defined	No

Appendix N. Quality Ratings of Studies of Adverse Effects of Risk Assessment and Testing Studies

Author, year	Adjustment for potential confounders?	Maintenance of comparable groups?	Important outcomes considered?	Reporting of attrition, contamination, etc.?	Differential loss to follow-up or overall high loss to follow-up?	Quality rating	External validity
Bish et al, 2002a[155]	No	N/A	Yes	Yes	No	Fair	Family cancer clinic, London
Bish et al, 2002b[164]	No	Yes	Yes	Yes	Yes	Poor	Family cancer clinic, London
Brain et al, 2002[156]	Yes	Yes	Yes	Yes	No	Good	Cancer clinics, Wales
Friedman et al, 1999[157]	No	Yes	Yes	Yes	High loss to follow-up No data on decliners	Fair	Highly educated Jewish persons in Houston, TX, community-based genetic testing program
Fry et al, 2003[165]	No	No	Yes	Participation bias present	High loss to follow-up	Poor	Women in SE Scotland referred to clinical genetics dept. for breast cancer genetic risk counseling

Appendix N. Quality Ratings of Studies of Adverse Effects of Risk Assessment and Testing Studies

Author, year	Study design	Random assignment?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Blinding: outcome assessors, care provider, patient?	Clear definition of measures?	Intention-to-treat analysis?
Gilbert et al, 1998[166]	Time series	Yes	N/A	N/A	Yes	N/A	Yes	N/A
Hopwood et al, 1998[158]	Non-comparative	No	N/A	N/A	Yes	N/A	Yes	N/A
Lerman et al, 1998[159]	Prospective cohort	No	N/A	N/A	Yes	N/A	Yes	N/A
Lobb et al, 2004[160]	Longitudinal	No	N/A	Yes	Yes	N/A	Yes	N/A
Lodder et al, 2002[167]	Prospective cohort	No	N/A	N/A	Yes	N/A	Yes	N/A

Appendix N. Quality Ratings of Studies of Adverse Effects of Risk Assessment and Testing Studies

Author, year	Adjustment for potential confounders?	Maintenance of comparable groups?	Important outcomes considered?	Reporting of attrition, contamination, etc.?	Differential loss to follow-up or overall high loss to follow-up?	Quality rating	External validity
Gilbert et al, 1998[166]	No	Not able to determine	Yes	Yes	Difficult to determine--data not given for + vs - family history	Poor	Women in NE Scotland in 3 health centers
Hopwood et al, 1998[158]	Yes	N/A	Yes	Yes	No	Good/ Fair	Women in Manchester, England, family genetics clinic
Lerman et al, 1998[159]	Adjustment for most potential confounders	Yes	Yes	Yes	30% of test decliners lost to follow-up	Fair	US hereditary breast/ovarian cancer registry composed of highly educated Caucasians
Lobb et al, 2004[160]	Yes	Yes	Yes	Yes	19% loss to follow-up	Good	Women in any of 10 familial cancer clinics in four Australian states
Lodder et al, 2002[167]	Incomplete	Not able to determine	Incomplete consideration	Yes	High loss to follow-up	Poor	Highly selected European women

Appendix N. Quality Ratings of Studies of Adverse Effects of Risk Assessment and Testing Studies

Author, year	Study design	Random assignment?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Blinding: outcome assessors, care provider, patient?	Clear definition of measures?	Intention-to-treat analysis?
Lodder et al, 2001[168]	Case-Control	No	N/A	Yes	Yes	N/A	Yes	N/A
Meiser et al, 2002[161]	Prospective cohort	No	N/A	Yes (analysis)	Yes	N/A	Yes	N/A
Meiser et al, 2001[169]	Before-After	No	N/A	N/A	Yes	N/A	Yes	N/A
Ritvo et al, 2000[170]	Prospective cohort	No	N/A	Incomplete information	General criteria for Cohort A; none for Cohort B	N/A	Not all were clearly defined	N/A
Smith et al, 1999[162]	Prospective cohort	No	N/A	Yes	Yes	N/A	Yes	Participation analysis

Appendix N. Quality Ratings of Studies of Adverse Effects of Risk Assessment and Testing Studies

Author, year	Adjustment for potential confounders?	Maintenance of comparable groups?	Important outcomes considered?	Reporting of attrition, contamination, etc.?	Differential loss to follow-up or overall high loss to follow-up?	Quality rating	External validity
Lodder et al, 2001[168]	Adjustment for some potential confounders	Yes	Yes	Yes	High loss to follow-up	Poor	Women who applied for *BRCA* testing at University Hospital, Rotterdam, and their partners
Meiser et al, 2002[161]	Potential confounders evaluated and were not significant	Yes	Yes	Yes	Overall follow-up 80%, by group 73% to 87%	Good	Women at 21 cancer clinics in Australia; more highly educated than general population
Meiser et al, 2001[169]	No	N/A	Yes	Yes	High loss to follow-up	Poor	Women at 21 cancer clinics in Australia; more highly educated than general population
Ritvo et al, 2000[170]	No	Incomplete information	No	Yes	Overall follow-up 77%; Cohort B follow-up 71%; d+N21rop-outs younger & less optimistic	Poor	Women at Toronto family cancer clinic seeking genetic risk assessment
Smith et al, 1999[162]	Yes	Difficult to assess due to attrition	Yes	Yes	High loss to follow-up	Fair	Members of kindred 2082, most of whom are Mormons

Appendix N. Quality Ratings of Studies of Adverse Effects of Risk Assessment and Testing Studies

Author, year	Study design	Random assignment?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Blinding: outcome assessors, care provider, patient?	Clear definition of measures?	Intention-to-treat analysis?
Warner et al, 2003[171]	Before-After	No	N/A	Yes	Yes	N/A	No	Participation analysis
Watson et al, 1999[163]	Before-After	No	N/A	Of 4 clinic sites, 1 had younger & 1 had higher risk women	Yes	N/A	Yes	N/A

Appendix N. Quality Ratings of Studies of Adverse Effects of Risk Assessment and Testing Studies

Author, year	Adjustment for potential confounders?	Maintenance of comparable groups?	Important outcomes considered?	Reporting of attrition, contamination, etc.?	Differential loss to follow-up or overall high loss to follow-up?	Quality rating	External validity
Warner et al, 2003[171]	No	Yes	No	Yes	High loss to follow-up	Poor	Women patients with family history of breast cancer recruited by their doctors who are mambers of Canada's CFPC
Watson et al, 1999[163]	Yes	Yes	Yes	Very low attrition	Low loss to follow-up Differential loss data not reported	Good	Women with a family history of breast cancer attending South London genetic clinic

CFPC, College of Family Physicians of Canada; RCT, randomized controlled trial.

Appendix O. Evidence Table of Chemoprevention Trials

Study	N	Population / Setting	Demographics	Inclusion / Exclusion criteria
Tamoxifen (20 mg per day)				
International Breast Cancer Intervention Study (IBIS-I) (IBIS, 2002)[59]	7,152	Women with increased risk for breast cancer recruited through family history clinics, relatives of women with breast cancer, breast screening centers, general practitioners, and media in UK, Australia, New Zealand	Mean age 50.8 years 54.7% between ages 45-54 60% from UK, 37% from Australia or New Zealand 49% postmenopausal and 41% had previously used HRT	Included if age 35-70 with risk factors (2-fold relative risk for ages 45-70, 4-fold relative risk for ages 40-44, 10-fold relative risk for ages 35-39 based on family history and other criteria).* Excluded if any previous invasive cancer (except non-melanoma skin cancer), previous DVT or pulmonary embolism, current use of anticoagulants, life expectancy <10 years, pregnant or planning pregnancy.
National Surgical Adjuvant Breast and Bowel Project P-1 Study (Fisher et al, 1998)[60]	#####	Women with increased breast cancer risk by age, Gail model risk, or history; recruited from multiple clinical centers in the US	Of 13,175 with follow-up: 2.6% 35-39 years old 39.3% 35-49 30.7% 50-59 30% 60 years or older 6% 70 years or older 96.4% white	Included if at increased risk for breast cancer due to 1) 60 years or older, 2) 35-59 years with 5-year predicted risk of at least 1.66% by Gail model, 3) history of lobular carcinoma in situ. Also must have 10 years life expectancy, no clinical evidence of cancer, not pregnant, normal white blood cell and platelet counts, normal hepatic and renal function, available for follow-up, have undergone endometrial sampling, taken no HRT oral contraception or androgens at least 3 months before, and no history of DVT or pulmonary embolism.

Appendix O. Evidence Table of Chemoprevention Trials

Study	Assignment and attrition	Monitoring
Tamoxifen (20 mg per day)		
International Breast Cancer Intervention Study (IBIS-I) (IBIS, 2002)[59]	3,574 placebo, 3,578 tamoxifen 3,528 (98.9%) placebo began treatment (8 excluded due to breast cancer at entry) 959 (26.9%) completed 5 years 3,523 (98.6%) tamoxifen began treatment (5 excluded due to breast cancer at entry) 837 (23.4%) completed 5 years Total of 7,139 included in analysis; median follow-up 50 months	All had baseline mammograms at time of randomization to exclude pre-existing cancer and a blood sample for cholesterol assays and marker studies. Mammograms were done every 12-18 months and blood samples at 1 year and 5 years. Follow-up was performed every 6 months during the 5 years of active treatment and by annual questionnaire or clinical visit thereafter for up to 5 years. Details of side-effects were collected at every visit. Concomitant medications were recorded.
National Surgical Adjuvant Breast and Bowel Project P-1 Study (Fisher et al, 1998)[60]	57,641 considered, 14,453 agreed to be medically evaluated for eligibility, 13,954 met eligibility requirements, 13,388 randomized (6,707 placebo, 6,681 tamoxifen). 13,175 had follow-up and were included in final analysis; median follow-up 55 months; 73.9% exceeded 36 months follow-up, 67% 48 months, and 36.8% 60 months.	Blood was obtained at entry for *BRCA1/BRCA2* mutation testing (see King et al, 2001[189]).

Appendix O. Evidence Table of Chemoprevention Trials

Study	Results	Adverse effects
Tamoxifen (20 mg per day)		
International Breast Cancer Intervention Study (IBIS-I) (IBIS, 2002)[59]	170 cases of breast cancer. All cases: 69 tamoxifen vs 101 placebo, RR=0.68, 0.50-0.92; Invasive: 64 tamoxifen vs 85 placebo, RR=0.75, 0.54-1.04; Non-invasive: 5 tamoxifen vs 16 placebo, RR=0.31; 0.12-0.82; Breast cancer deaths: 2 in each group. Highest risk among women with two or more 1st- or 2nd-degree relatives with breast cancer (62%). Yearly frequency of breast cancer for placebo group was 6.74 per 1,000 (projected 7.5 per 1,000).	Endometrial cancer (11 tamoxifen vs 5 placebo; RR=2.2, 0.8-6.06); most in women >50 years old at randomization (10 tamoxifen, 3 placebo); all postmenopausal at diagnosis; no deaths from endometrial cancer. Venous thromboembolic events (43 tamoxifen vs 17 placebo; RR=2.5, 1.5-4.4). Most risk and all deaths from thromboembolic events on tamoxifen occurred after surgery. All cause death rate (25 tamoxifen vs 11 placebo, p=0.028). Vasomotor/gynecological problems 21% higher on tamoxifen than placebo, breast complaints 22% lower. Increased hot flushes, vaginal discharge, abnormal vaginal bleeding on tamoxifen. Hysterectomy rate 2.7% on placebo, 4.2% on tamoxifen (p=0.002). Ovarian cysts and amenorrhea more than 2 times as common on tamoxifen in premenopausal women.
National Surgical Adjuvant Breast and Bowel Project P-1 Study (Fisher et al, 1998)[60]	175 invasive breast cancer cases in placebo vs 89 in tamoxifen groups (RR=0.51, 0.39-0.66). 69 non-invasive cases in placebo vs 35 in tamoxifen (RR=0.50, 0.33-0.77). Decreased risk occurred in women 49 years and younger (44%), 50-59 years (51%), and 60 years or older (55%). Tamoxifen reduced ER positive tumors but not ER negative.	Rate of endometrial cancer was increased in tamoxifen group (RR=2.2, 0.8-6.06), predominantly in women 50 years or older, no deaths. Rates of venous thromboembolic events were elevated in tamoxifen group (RR=2.5, 1.5-4.4) occurring more frequently in women age 50 and older.

Appendix O. Evidence Table of Chemoprevention Trials

Study	N	Population / Setting	Demographics	Inclusion / Exclusion criteria
Tamoxifen (20 mg per day)				
Royal Marsden Hospital Trial (Powles et al, 1998)[61]	2,508	Women with a family history of breast cancer; Royal Marsden Hospital, UK	Median age: 47 years <50: 774 tamoxifen, 749 placebo Pre/perimenopausal: 822 tamoxifen, 812 placebo Postmenopausal: 416 tamoxifen, 421 placebo On HRT at start: 187 tamoxifen, 202 placebo	Included if healthy aged 30-70 years with increased risk due to family history of breast cancer,† no evidence of breast cancer at entry to trial. Postmenopausal HRT allowed. Excluded if any history of cancer, DVT, or pulmonary embolism. Premenopausal women considering pregnancy or taking oral contraception were also excluded.
Italian Tamoxifen Prevention Study (Veronesi et al, 1998)[62]	5,408	Women with hysterectomies from 55 participating centers, of which 51 were in Italy (5,230 patients, 97%), 3 in South America, and 1 in Greece	Median age: 51 5,287 (98.3%) total hysterectomy; 1,412 (26.3%) ovary conservation; 2,595 (48.3%) bilateral oopherectomy; 998 (18.6%) unilateral oophorectomy; 282 (5.2%) no information available	Included if healthy aged 35-70 years without breast cancer and had a hysterectomy. Excluded if severe concurrent illness or history of cardiac disease, endometriosis, and suspected or certain previous DVT.

Appendix O. Evidence Table of Chemoprevention Trials

Study	Assignment and attrition	Monitoring
Tamoxifen (20 mg per day)		
Royal Marsden Hospital Trial (Powles et al, 1998)[61]	14 withdrew before randomization, 2,494 randomized: 1,250 tamoxifen (12 excluded from analysis), 1,244 placebo (11 excluded from analysis) 2,471 used in analysis: 1,238 tamoxifen, 1,233 placebo; median follow-up 70 months	Follow-up every 6 months included clinical examination and assessment of toxicity and compliance; mammography annually. Compliance assessed by direct questioning and checked against random blood testing. Serum cholesterol measured before treatment and every 6 months thereafter. Blood samples collected from 1992 for future genetic testing.
Italian Tamoxifen Prevention Study (Veronesi et al, 1998)[62]	4,989 refused, 1,499 ineligible, 527 not contactable, 996 missing 5,408 randomized (2,708 placebo, 2,700 tamoxifen) 3,837 took assigned medication (1,966 placebo, 1871 tamoxifen) 149 completed 5 years treatment; median follow-up 46 months	Follow-up during treatment included minimum of twice-yearly assessment of side-effects and compliance; mammograms annually.

Appendix O. Evidence Table of Chemoprevention Trials

Study	Results	Adverse effects
Tamoxifen (20 mg per day)		
Royal Marsden Hospital Trial (Powles et al, 1998)[61]	Breast cancer incidence was the same for tamoxifen and placebo (34 tamoxifen, 36 placebo, NS); of these, 8 were non-invasive (4 each group). No interaction between use of HRT and effect of tamoxifen on breast cancer occurrence (12/523 HRT on tamoxifen, 13/507 HRT on placebo, p=0.6) Those who started HRT while in study had significantly reduced risk. Nulliparous women had 2-fold increase in risk of breast cancer compared with women with children.	Occurrence of adverse events was low. For endometrial cancer: 4 cases tamoxifen, 1 placebo, NS. 156 completed 8 years medication; 877 stopped prematurely for non-toxic reasons or side-effects (320 tamoxifen, 176 placebo, p<0.0005). 336 tamoxifen and 305 placebo required HRT during study. 280 (11%) lost to follow-up for over 18 months.
Italian Tamoxifen Prevention Study (Veronesi et al, 1998)[62]	No difference in breast cancer occurrence between placebo (22) and tamoxifen (19); no breast cancer deaths. Statistically significant reduction among women taking tamoxifen and HRT during trial: among 390 women on HRT assigned to placebo, 8 cases of breast cancer vs 1 case in 362 on tamoxifen. No difference in effects of tamoxifen between women <50 years (p=0.72) and women >50 years (p=0.77). No difference in frequency of ER positive breast cancer between tamoxifen (10) and placebo (8).	Significantly increased risk of vascular events and hypertriglyceridemia among women on tamoxifen. 56 women experienced vascular events, 18 placebo, 38 tamoxifen (p=0.0053); 42 were superficial phlebitis, and 9 diagnosed with DVT (6 tamoxifen, 3 placebo).

Appendix O. Evidence Table of Chemoprevention Trials

Study	N	Population / Setting	Demographics	Inclusion / Exclusion criteria
Raloxifene (60 or 120 mg per day)				
Multiple Outcomes of Raloxifene Evaluation (Cummings et al, 1999)[64]	7,705	Postmenopausal women with osteoporosis recruited from 180 clinical centers in 25 countries, including US and Europe.	Mean age 66.6 placebo 66.4 raloxifene 95.7% white for both groups Current smoker 16.5% placebo 16.9% raloxifene Family history of breast cancer 12.1% placebo 12.4% raloxifene	Included if at least 2 years postmenopausal, 80 years or younger, with osteoporosis, not on HRT. Excluded if had known, suspected, or history of breast cancer, invasive endometrial cancer, abnormal uterine bleeding, history of stroke or venous thromboembolic disease during past 10 years, any type of cancer (other than superficial skin cancer in previous 5 years), secondary causes of osteoporosis, or other bone diseases.

Appendix O. Evidence Table of Chemoprevention Trials

Study	Assignment and attrition	Monitoring
Raloxifene (60 or 120 mg per day)		
Multiple Outcomes of Raloxifene Evaluation (Cummings et al, 1999)[64]	7,705 randomized 2,576 placebo 5,129 raloxifene 2,557 took 60 mg 2,572 took 120 mg 6,932 (90%) continued past first annual visit (6,333 [91%] had mammogram and 177 [3%] had breast sonography) 6,381 (83%) continued past second annual visit (5,642 [88%] had mammogram and 176 [3%] had breast sonography) Continued past 36 months 1,924 (75%) placebo 3,977 (78%) raloxifene; median follow-up 40 months.	All provided with daily supplements: 500 mg calcium and 400-600 IU of cholecalciferol. Mammograms were optional after 1st year, but required after 2 and 3 years of treatment. Women who refused mammograms were offered breast ultrasound. Annual transvaginal ultrasonography was performed in 17 designated centers for all women with an intact uterus. Subsets of patients received this exam at other centers. Endometrial biopsies were recommended for women with symptoms of vaginal bleeding, endometrial thickness >8 mm on ultrasound, or with increases in endometrial thickness of at least 5 mm.

Appendix O. Evidence Table of Chemoprevention Trials

Study	Results	Adverse effects
Raloxifene (60 or 120 mg per day)		
Multiple Outcomes of Raloxifene Evaluation (Cummings et al, 1999)[64]	56 cases of breast cancer were reported, 54 confirmed; 12 classified as in situ, 40 classified as invasive, insufficient information to classify 2 cases. 13 cases of invasive breast cancer on raloxifene and 27 on placebo occurred by the end of the trial (RR=0.24, 0.13-0.44). Raloxifene was associated with a decrease in ER positive but not ER negative cancers. Approximately 126 women would need to be treated for a median of 40 months to prevent 1 case of invasive cancer.	By 40 months, higher rates of DVT (38 cases, 0.7%) and pulmonary embolus (17 cases, 0.3%) on raloxifene than placebo (5 cases, 0.2%; 3 cases, 0.1% respectively). Risk of venous thromboembolic disease higher on raloxifene than placebo (RR=3.1, 1.5-6.2). Among 5,957 women who had not had a hysterectomy, endometrial cancer occurred in 4 (0.20%) on placebo and 6 (0.25%) on raloxifene.

Appendix P. Quality Ratings of Chemoprevention Trials

Author, year	Adequate random-ization?	Blinding?	Maintenance of comparable groups?	Loss to follow-up?	Measures equal, reliable, valid?	Clear definition of interven-tions?	Important outcomes consider-ed?	Intention-to-treat analysis?	Quality rating for internal validity	Quali rating exterr validi
IBIS, 2002[59]	Yes	Yes	More stopped tamoxifen than placebo due to side effects	77% loss in tamoxifen and 73% loss in placebo group at 60 months	Yes	Yes	Yes	Yes	Fair to good	Good fo similar higher r women
Fisher et al, 1998[60]	Yes	Yes	Yes; loss to follow-up similar	33% loss at >48 months; 63% loss at >60 months	Yes	Yes	Yes	Yes	Fair to good	Good fo similar higher r women
Powles et al, 1998[61]	Yes	Yes	More stopped tamoxifen than placebo due to side effects	42% loss at 70 months	Yes	Yes	Yes	Yes	Fair to good	Good fo similar higher r women
Veronesi et al, 1998[62]	Not provided	Yes	Not provided	96% loss at 60 months	Yes	Yes	Yes	Yes	Fair	Fair; women study have hystere omy

Appendix P. Quality Ratings of Chemoprevention Trials

Author, year	Adequate random-ization?	Blinding?	Maintenance of comparable groups?	Loss to follow-up?	Measures equal, reliable, valid?	Clear definition of interven-tions?	Important outcomes consider-ed?	Intention-to-treat analysis?	Quality rating for internal validity	Quali rating exterr validi
Cummings et al, 1999[64]	Yes	Yes	More stopped raloxifene than placebo due to side effects	22% of raloxifene, 25% of placebo with loss to follow-up at 36 months	Yes	Yes	Yes	Yes	Good	Fair; women study have osteopo osis

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*Criteria for enrollment in the high-risk category (must meet at least one of these criteria)
Two or more first-degree relatives with breast cancer
One first-degree relative and two or more second or third-degree relatives with breast cancer
One first-degree relative with breast cancer before the age of 45 years and one other relative with breast cancer
One first-degree relative with breast cancer and one or more relatives with ovarian cancer
Two second or third-degree relatives with breast cancer and one or more with ovarian cancer
One second or third-degree relative with breast cancer and two or more with ovarian cancer
Three or more second or third-degree relatives with breast cancer
One first-degree relative with bilateral breast cancer

Criteria for enrollment in the moderate-risk category
Women with a relative with breast cancer who do not meet above criteria

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Appendix R. Quality Ratings of Prophylactic Studies

Author, year	Design	Considers potential confound-ers?	Mainten-ance of compar-able groups?	Loss to follow-up?	Measures equal, reliable, valid?	Clear definition of interven-tions?	Important outcomes considered?	Adjust-ment for confound-ers?	Quality rating for internal validity	Qualit rating f extern validit
Mastectomy										
Hartmann et al, 1999[201]	Retrospec-tive cohort with comparison group	Yes	Yes	No	Yes	Yes	Yes	Limited	Study design not included in USPSTF quality criteria	Highl selecte wome
Hartmann et al, 2001[202]	Retrospec-tive cohort	Yes	Yes	No	Yes	Yes	Yes	Limited	Fair	Highl selecte wome

Appendix R. Quality Ratings of Prophylactic Studies

Author, year	Design	Considers potential confound-ers?	Mainten-ance of compar-able groups?	Loss to follow-up?	Measures equal, reliable, valid?	Clear definition of interven-tions?	Important outcomes considered?	Adjust-ment for confound-ers?	Quality rating for internal validity	Qualit rating f extern validit
Meijers-Heijboer et al, 2001[70]	Prospective cohort	Yes	Yes	No	Yes	Yes	Yes	Limited	Fair	Highl selecte wome
Rebbeck et al, 2004[71]	Prospective & retrospec-tive cohort with matched comparison group	Yes	Yes	No	Yes	Yes	Yes	Limited	Study design not included in USPSTF quality criteria	Highl selecte wome
Oophorectomy										
Rebbeck et al, 1999[72]	Prospective & retrospec-tive cohort with matched comparison group	Yes	Yes	No	Yes	Yes	Yes	Limited	Study design not included in USPSTF quality criteria	Highl selecte wome

Appendix R. Quality Ratings of Prophylactic Studies

Author, year	Design	Considers potential confound-ers?	Mainten-ance of compar-able groups?	Loss to follow-up?	Measures equal, reliable, valid?	Clear definition of interven-tions?	Important outcomes considered?	Adjust-ment for confound-ers?	Quality rating for internal validity	Qualit rating f extern validit
Rebbeck, 2002[73]	Retrospec-tive cohort with matched comparison group	Yes	Yes	No	Yes	Yes	Yes	Limited	Study design not included in USPSTF quality criteria	Highl selecte wome
Kauff et al, 2002[74]	Prospective cohort	Yes	Yes	No	Yes	Yes	Yes	Limited	Fair	Highl selecte wome

USPSTF, U.S. Preventive Services Task Force.

Appendix S. Sensitivity Analyses

Assumptions	Risk level Moderate	Risk level High
Number of women screened	100,000	100,000
Prevalence of clinically significant *BRCA* mutations (%)		
BRCA1	0.82(0.53 - 1.28)	6.42(1.13 - 29.09)
BRCA2	1.13(0.88 - 1.44)	1.1(0.61 -1.98)
Penetrance of mutation to age 40/50 (%)		
Breast cancer (to age 40 years)		
BRCA1	5.03(1.85,12.97)	6.88(1.92-21.78)
BRCA2	1.23(0.40-3.75)	9.1(4.11-18.94)
Ovarian cancer (to age 50 years)[#]		
BRCA1	14.16(9.17-21.23)	no data
BRCA2	1.79(0.88, 3.58)	no data
Penetrance of mutation to age 75 (%)		
Breast cancer		
BRCA1	38.83(27.26-51.80)	44.14(11.47-82.82)
BRCA2	24.89(13.11-42.14)	24.17(17.20-32.84)
Ovarian cancer[#]		
BRCA1	31.49(21.91-42.96)	21.67(4.84-60.07)
BRCA2	11.72(8.16 -16.56)	44.57(28.06-62.37)
Risk reduction of SERMs to prevent all types of breast cancer, trials with mutation status unknown (RR=0.62; 0.46-0.83)	0.38(0.17 - 0.54)	0.38(0.17 - 0.54)
Risk of thromboembolic events from SERMs (% per year)	0.096(0.036-0.156)	0.096(0.036-0.156)
Risk of endometrial cancer from SERMs (% per year)	0.036 (0.00177 - 0.0709)	0.036 (0.00177 - 0.0709)
Proportion of candidates choosing SERMs (%) (not known)	uniform(5,50)	uniform(5,50)

Appendix S. Sensitivity Analyses

Risk reduction of mastectomy to prevent breast cancer if *BRCA* mutation (RR=0; 0-0.36)	0.91(0.64-1.00)	0.91(0.64-1.00)
Risk of complications from mastectomy and reconstruction (% overall) (based on one study; range not known)	21	21
Proportion of candidates choosing mastectomy (%) (not known)	uniform(5,20)	uniform(5,20)
Risk reduction of oophorectomy to prevent breast cancer if *BRCA* mutation (RR=0.32; 0.08-1.20)	0.68(0.01-0.92)	0.68(0.01-0.92)
Risk of complications from oophorectomy (% overall) (based on one study; range not known)	5	5
Proportion of candidates choosing oophorectomy (%) (not known)	uniform(25,75)	uniform(25,75)

Appendix S. Sensitivity Analyses

Assumptions (continued)	Risk level Moderate	Risk level High
Risk reduction of oophorectomy to prevent ovarian cancer in *BRCA* mutation ((RR-0.15; 0.02-2.31)	0.85 (0.01-0.99)	0.85 (0.01-0.99)
Risk of complications from oophorectomy (% overall) (based on one study; range not known)	5	5
Proportion of candidates choosing oophorectomy (%) (not known)	uniform(25,75)	uniform(25,75)
Outcomes–benefits to age 40	**Risk level moderate**	**Risk level High**
Number of breast cancer cases expected among candidates if not undergoing treatment	58(26-126)	467(158,1707)
Number of breast cancer cases prevented among candidates taking SERMs (using overall risk reduction of 0.38)	5.4(0.93-18.3)	43(6.3-219)
NNS to prevent 1 case of breast cancer using SERMs	18677(5466-108044)	2344(456-15930)
NNT with SERMs to prevent 1 case of breast cancer	92(37-273)	44(11-164)
Number of breast cancer cases prevented among candidates undergoing mastectomy	6.3(1.9-17.3)	50(12-217)
NNS to prevent 1 case of breast cancer using mastectomy	15988(5771-51294)	1987(460-8076)
NNT with mastectomy to prevent 1 case of breast cancer	37.1(16.7-85.4)	17.8(4.8-54)
Number of breast cancer cases prevented among candidates if undergoing oophorectomy	16.7(0.27-51.6)	134(2.1 - 633)
NNS to prevent 1 case of breast cancer using oophorectomy	5924(1940-371335)	747(158-46855)
NNT with oophorectomy to prevent 1 case of breast cancer	54(21.2 - 3463)	27(6.3-1693)
Number of ovarian cancer cases expected among candidates if not undergoing treatment	138(94-198)	No data

Number of ovarian cancer cases prevented among candidates undergoing oophorectomy	51(0.62-107)	No data
NNS to prevent 1 case of ovarian cancer using oophorectomy	1968(934-161826)	No data
NNT with oophorectomy to prevent 1 case of ovarian cancer	17.7(11.1-1476)	No data

Outcomes–benefits to age 75	**Risk level Moderate**	**Risk level High**
Number of breast cancer cases expected among candidates if not undergoing treatment	604(433-820)	3465(1361 -5955)
Number of breast cancer cases prevented among candidates taking SERMs (using overall risk reduction of 0.38)	58(11-143)	306(51-971)
NNS to prevent 1 case of breast cancer using SERMs	1739(697-8814)	327(103 - 1945)
NNT with SERMs to prevent 1 case of breast cancer	8.6(5.3-20.6)	6.0(2.9-19.6)
Number of breast cancer cases prevented among candidates undergoing mastectomy	67(26-128)	360(105-894)
NNS to prevent 1 case of breast cancer using mastectomy	1497(783-3801)	278(112-952)
NNT with mastectomy to prevent 1 case of breast cancer	3.5(2.5-5.6)	2.4(1.3-6.3)
Number of breast cancer cases prevented among candidates if undergoing oophorectomy	181(2.9-395)	972(16-2710)
NNS to prevent 1 case of breast cancer using oophorectomy	554(253-34512)	103(37-6395)
NNT with oophorectomy to prevent 1 case of breast cancer	4.9(3.0-327)	3.6(1.6-223)
Number of ovarian cancer cases expected among candidates if not undergoing treatment	393(302-499)	1888(782-4357))

Appendix S. Sensitivity Analyses

Number of ovarian cancer cases prevented among candidates undergoing oophorectomy	146(1.8-286)	668(7.9 - 2110)
NNS to prevent 1 case of ovarian cancer using oophorectomy	687(350-56591)	150(47 - 12658)
NNT with oophorectomy to prevent 1 case of ovarian cancer	6.1(4.3-512)	5.3(2.0 - 447)

Appendix S. Sensitivity Analyses

Outcomes–adverse effects	Risk level Moderate	Risk level High
Number of women taking SERMs	544(119-1044)	1893(292-9885)
Number of cases of thrombotic events due to SERMs	0.52(0.088-1.24)	2.59(0.22-10.1)
NNT with SERMs to cause one thrombotic event	1042(641-2719)	1042(641-2719)
Number of cases of endometrial cancer due to SERMs	0.20(0.0068-0.54)	0.98(0.019-4.14)
NNT with SERMs to cause one case of endometrial cancer	2686(1228-15726)	2686(1228-15726)
Number of women undergoing mastectomy	247(102-424)	897(201-4176)
Number of women with complications from	52.0(21.4-89.0)	188(42-877)
NNT with mastectomy to cause one complication	5	5
Number of women undergoing oophorectomy	990(490-1601)	3651(901-16246)
Number of women with complications from oophorectomy	49.5(24.5-80.0)	183(45-812)
NNT oophorectomy to cause one complication	20	20

NNS, number needed to screen; NNT, number needed to treat; SERMs, selective estrogen receptor modulators.