Genetic Risk Assessment and *BRCA* Mutation Testing for Breast and Ovarian Cancer Susceptibility: Systematic Evidence Review for the U.S. Preventive Services Task Force

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Background: **Clinically significant mutations of *BRCA1* and *BRCA2* genes are associated with increased susceptibility for breast and ovarian cancer. Although these mutations are uncommon, public interest in testing for them is growing.**

Purpose: **To determine benefits and harms of screening for inherited breast and ovarian cancer susceptibility in the general population of women without cancer presenting for primary health care in the United States.**

Data Sources: **MEDLINE (1966 to 1 October 2004), Cochrane Library databases, reference lists, reviews, Web sites, and experts.**

Study Selection: **Eligibility was determined by inclusion criteria specific to key questions about risk assessment, genetic counseling, mutation testing, prevention interventions, and potential adverse effects.**

Data Extraction: **After review of studies, data were extracted, entered into evidence tables, and summarized by using descriptive or statistical methods. Study quality was rated by using predefined criteria.**

Data Synthesis: **Tools assessing risks for mutations and referral guidelines have been developed; their accuracy, effectiveness, and adverse effects in primary care settings are unknown. 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. Intensive cancer screening studies are inconclusive. Chemoprevention trials indicate risk reduction for breast cancer in women with varying levels of risk, as well as increased adverse effects. Observational studies of prophylactic surgeries report reduced risks for breast and ovarian cancer in mutation carriers.**

Limitations: **No data describe the range of risk associated with *BRCA* mutations, genetic heterogeneity, and moderating factors; studies conducted in highly selected populations contain biases; and information on adverse effects is incomplete.**

Conclusions: **A primary care approach to screening for inherited breast and ovarian cancer susceptibility has not been evaluated, and evidence is lacking to determine benefits and harms for the general population.**

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Clinically significant, or deleterious, mutations of *BRCA1* and *BRCA2* genes are associated with increased susceptibility for breast and ovarian cancer (1, 2). These mutations increase a woman's lifetime risk for breast cancer to 60% to 85% (3, 4) and risk for ovarian cancer to 26% (*BRCA1)* and 10% (*BRCA2*) (5–8). Specific *BRCA* mutations are clustered among certain ethnic groups, such as Ashkenazi Jews (9–11), and in the Netherlands (12), Iceland (13, 14), and Sweden (15). Additional germline mutations associated with familial breast or ovarian cancer have been identified, and others are suspected (16, 17). *BRCA1* and *BRCA2* mutations are also associated with increased risk for prostate cancer, and *BRCA2* mutations are associated with increased risk for pancreatic and stomach cancer and melanoma (18).

Screening for inherited breast and ovarian cancer susceptibility is a 2-step process: assessment of risk for clinically significant *BRCA* mutations followed by genetic testing of high-risk individuals. Guidelines recommend testing for mutations only when an individual has personal or family history features suggestive of inherited cancer susceptibility, when the test result can be adequately interpreted, and when results will aid in management (19, 20).

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Table 1. **Detection and Prevention Recommendations**

Intervention	Average-Risk Women*	High-Risk Women*
Breast cancer screening	Annual mammography every 1–2 y beginning at age 40 y (36)	*BRCA* mutation carriers: monthly self-examinations beginning by age 18–21 y, annual or semiannual clinician examinations beginning at age 25–35 y, and annual mammography beginning at age 25–35 y (37)
Ovarian cancer screening	No screening (38)	*BRCA1* mutation carriers: annual or semiannual screening using transvaginal ultrasonography and CA-125 serum levels beginning at age 25–35 y; optional for *BRCA2* mutation carriers (37, 39)
Chemoprevention for breast cancer	None (40)	Women at increased risk for breast cancer as defined by the Gail model and low risk for complications: tamoxifen chemoprophylaxis (40)
Prophylactic mastectomy and oophorectomy	None	Women with ≥2 first-degree relatives with ovarian cancer: offer prophylactic oophorectomy after completion of childbearing or at age 35 y (39)

* Numbers in parentheses are reference citations.

Several characteristics are associated with an increased likelihood of clinically significant *BRCA* mutations, including young age at breast cancer diagnosis, bilateral breast cancer, history of both breast and ovarian cancer, multiple cases of breast cancer in a family, both breast and ovarian cancer in a family, and Ashkenazi Jewish heritage (21–24). Risk status requires reevaluation when personal or family cancer history changes. Genetic counseling is recommended before mutation testing (25). Several approaches are in practice, including educational; decision-making; and psychosocial support (26, 27) provided by genetic counselors (28–30), nurse educators (31–33), or other professionals.

The type of mutation analysis required depends on family history. Individuals from families or ethnic groups with known mutations can be tested specifically for them. Several clinical laboratories in the United States test for specific mutations or sequence-specific exons. Individuals without linkages to others with known mutations undergo direct DNA sequencing. In these cases, guidelines recommend that testing begin with a relative who has known breast or ovarian cancer to determine whether a clinically significant mutation is segregating in the family (19). Myriad Genetic Laboratories provides direct DNA sequencing in the United States and reports analytic sensitivity and specificity exceeding 99% (34). Approximately 12% of high-risk families without a *BRCA1* or *BRCA2* coding-region mutation may have other clinically significant genomic rearrangements (34, 35). Test results include not only positive (denoting a deleterious mutation) and negative (no mutation found) interpretations but also variants of uncertain clinical significance; this last group represents up to 13% of results (21). The results of genetic testing could lead to prevention interventions for reducing risk or mortality in mutation carriers. Experts recommend earlier and more frequent cancer screening, chemoprevention, and prophylactic surgery (**Table 1**) (36–40).

Although clinically significant *BRCA* mutations are estimated to occur in 1 in 300 to 500 persons in the general population (41–44), public interest in testing is growing, and physicians are increasingly faced with this issue while providing primary health care. Women often overestimate their risks for breast cancer or *BRCA* mutations (32, 45, 46), and most women responding to surveys, including women at average and moderate risk, report a strong desire for genetic testing (27, 47), even though only those at high risk would potentially benefit. Concerns about cancer, publicized scientific advances, incomplete understanding of testing and interventions, and direct-to-consumer advertising probably influence these perceptions, increasing demand for genetic testing services (47).

The objective of this systematic evidence review is to determine the benefits and harms of screening for inherited breast and ovarian cancer susceptibility in the general population of women presenting for primary health care in the United States. This review was prepared for the U.S. Preventive Services Task Force (USPSTF) and examines a chain of evidence about genetic risk assessment in primary care settings; impact of genetic counseling; ability to predict cancer risk in women with average, moderate, and high risks for clinically significant mutations; benefits of prevention interventions; and potential adverse effects. A review of studies about Ashkenazi Jewish women specifically is reported elsewhere (48).

METHODS

The analytic framework in **Figure 1** outlines the patient population, interventions, and health outcomes. This report focuses on the following key questions:

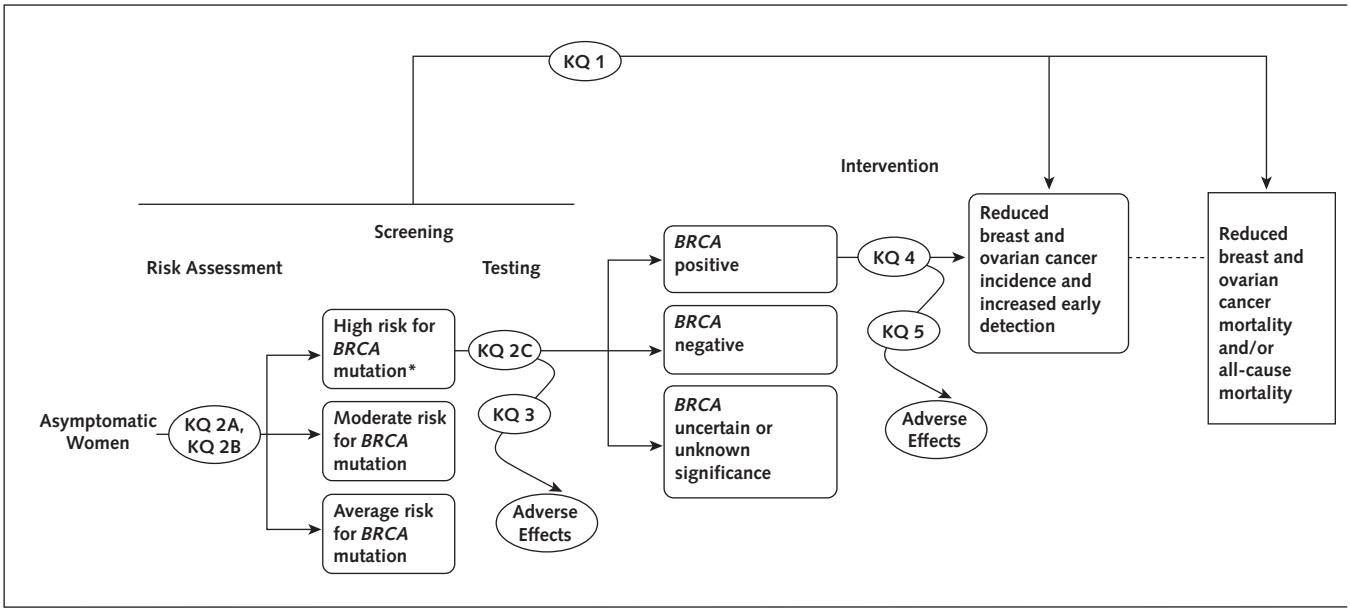
1. Do risk assessment and *BRCA* mutation testing lead to a reduction in the incidence of breast and ovarian cancer and cause-specific or all-cause mortality?

2A. How well does risk assessment for cancer susceptibility by a clinician in a primary care setting select candidates for *BRCA* mutation testing?

2B. What are the benefits of genetic counseling before testing?

2C. Among women with family histories predicting an

Figure 1. **Analytic framework.**



Key question (*KQ*) 1: Do risk assessment and *BRCA* mutation testing lead to a reduction in the incidence of breast and ovarian cancer and cause-specific or all-cause mortality? KQ 2A: How well does risk assessment for cancer susceptibility by a clinician in a primary care setting select candidates for *BRCA* mutation testing? KQ 2B: What are the benefits of genetic counseling before testing? KQ 2C: Among women with family histories predicting an average, moderate, or high risk for a deleterious mutation, how well does *BRCA* mutation testing predict risk for breast and ovarian cancer? KQ 3: What are the adverse effects of risk assessment, genetic counseling, and testing? KQ 4: 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? KQ 5: What are the adverse effects of interventions? *Indicates clinically significant mutation of *BRCA1* or *BRCA2*.

average, moderate, or high risk for a deleterious mutation, how well does *BRCA* mutation testing predict risk for breast and ovarian cancer?

3. What are the adverse effects of risk assessment, genetic counseling, and testing?

4. 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?

5. What are the adverse effects of interventions?

We identified relevant papers from multiple searches of MEDLINE (1966 to 1 October 2004) and the Cochrane Library databases; we obtained additional papers by reviewing reference lists of pertinent studies, reviews, editorials, and Web sites and by consulting experts (**Appendix Figure**, available at www.annals.org). Investigators reviewed all abstracts and determined eligibility by applying inclusion and exclusion criteria specific to key questions (**Appendix Table**, available at www.annals.org). We then reviewed full-text papers of included abstracts for relevance. Studies about patients with current or past breast or ovarian cancer were excluded unless they addressed genetic testing issues in women without cancer. Data were extracted from each included study, entered into evidence tables, and summarized by using descriptive or statistical methods or both. Two reviewers independently rated the quality of studies using criteria specific to different study designs developed by the USPSTF (Appendix 1, available at www.annals.org) (49). When reviewers disagreed, a final rating was determined by reevaluations by the 2 initial reviewers and a third reviewer if needed. Only studies rated good or fair in quality were included, although studies with designs that do not have quality rating criteria, such as descriptive studies, were also included if relevant to the key questions.

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 being a mutation carrier 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 1 second-degree relative on each side of the family with breast or ovarian cancer; moderate risk—1 first-degree relative or 2 second-degree relatives on the same side of the family with breast or ovarian cancer; and high risk—at least 2 first-degree relatives with breast or ovarian cancer. On the basis of pooled data from more than 100 000 women without breast cancer from 52 epidemiologic studies, approximately 92.7% of the screening population would be expected to be average risk, 6.9% moderate risk, and 0.4% high risk according to these definitions (50).

Risks for breast and ovarian cancer in mutation carriers have been primarily calculated from families of women with existing breast and ovarian cancer. To determine benefits and adverse effects of genetic testing in average-, mod-

erate-, and high-risk groups, we estimated mutation prevalence as well as the probability of developing cancer given the presence of the mutation (penetrance) 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 or ovarian cancer in the U.S. population estimated from Surveillance, Epidemiology, and End Result (SEER) data (51) by using DevCan software (52); and relative risks for breast and ovarian cancer in moderate- and high-risk groups. Penetrance estimates were based on the Bayes theorem and stratified by cancer type (breast or ovarian), risk group (average, moderate, and high), and age whenever data were available. Appendix 2 (available at www.annals.org) provides additional details of this method (48).

We also performed a meta-analysis of chemoprevention trials to more precisely estimate 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

Table 2. **Tools To Assess Risk for *BRCA* Mutation**

Tool (Mutation)	Study, Year (Reference)	Administration	Applications	Description
Myriad Genetics Laboratories model (*BRCA1*)	Shattuck-Eidens et al., 1997 (23)	Questions	Families with small numbers of affected members.	Logistic regression model developed from data from women with breast cancer, ovarian cancer, or a family history of breast and/or ovarian cancer. Probability estimates for individuals without cancer must be extrapolated from the model.
Myriad Genetics Laboratories model (*BRCA1* and *BRCA2*)	Frank et al., 1998 (57); Srivastava et al., 2001 (22)	Questions	Families with multiple members with early-onset breast cancer or ovarian cancer.	Logistic regression model developed from data from women with early-onset breast cancer, or ovarian cancer at any age, and ≥1 first- or second-degree relative with early-onset breast or ovarian cancer. Probability estimates for individuals without cancer must be extrapolated from the model.
Couch model (*BRCA1*)	Couch et al., 1997 (24); Blackwood et al., 2001 (58)	Questions	Families with ≥2 cases of breast or ovarian cancer.	Logistic regression model based on data from women with breast cancer. Updated model includes both *BRCA1* and *BRCA2*. Probability estimates for individuals without cancer must be extrapolated from the model.
BRCAPRO (*BRCA1* and *BRCA2*)	Berry et al., 1997 (59), 2002 (60); Parmigiani et al., 1998 (61); Euhus et al., 2002 (62), 2004 (63); CancerGene (64)	Computer program	Individuals with or without breast or ovarian cancer; applicable to a variety of families.	Bayesian model using first- and second-degree family history, including breast cancer, ovarian cancer, age at diagnosis, ethnicity, and size of family, to estimate the age-specific probability of finding a *BRCA* mutation. Generates conditional or posterior probabilities. Validated in populations with families with breast cancer.
Cyrillic 3 Software Program (*BRCA1* and *BRCA2*)	www.cyrillicsoftware.com (65)	Computer program (BRCAPRO and MENDEL)	Not reported	Integrated risk assessment allows creation of pedigrees using individual, family, and disease data.
Progeny Software Program (*BRCA1* and *BRCA2*)	www.progeny2000.com (71)	Computer program	Not reported	Allows creation of pedigrees using individual, family, and disease data.
Unnamed (*BRCA1* and *BRCA2*)	Tyrer et al., 2004 (66)	Computer program	Applicable to a variety of families	Bayesian model incorporating family cancer history and personal risk factors to produce a likelihood of carrying a clinically significant mutation and a risk estimate for developing breast cancer.
Family History Risk Assessment Tool (FHAT) (*BRCA1* and *BRCA2*)	Gilpin et al., 2000 (67)	Questions	Primary care population	Points are assigned according to the number of relatives, third-degree or closer, with breast, ovarian, colon, or prostate cancer, and the relationship to the proband, age at diagnosis, and type and number of cases of primary cancer. Scores ≥10 points warrant referral (equivalent to doubling of the general population lifetime risk for breast or ovarian cancer).
Risk Assessment in Genetics (RAGs) (*BRCA1* and *BRCA2*)	Emery et al., 1999, 2000, 2001 (69, 70, 72)	Computer program	Primary care population	Generates pedigrees using information about the proband and relatives, categorizes risks for breast and ovarian cancer, provides referral guidelines, and suggests appropriate management. One of 3 risk levels is assigned: low (<10% risk for having a clinically significant *BRCA1* or *BRCA2* mutation), patient is reassured and managed in primary care; moderate (10%–25% risk), patient is referred to a breast clinic; and high (>25% risk), patient is referred to a clinical geneticist.
Manchester Model (*BRCA1* and *BRCA2*)	Evans et al., 2004 (68)	Questions	Primary care population	Points are assigned according to the number of relatives with breast, ovarian, prostate, or pancreatic cancer, relationship to the proband, and age at diagnosis. Developed such that a score of 10 is equivalent to a 10% chance of identifying a *BRCA1* or a *BRCA2* mutation.

Table 3. **Criteria for Referral for Genetic Counseling and Testing***

Criteria Supporting Referral for Genetic Counseling for Breast and Ovarian Cancer	HMO Sites (74)†					Other Groups									
	A	B	C	D	E	NCCN High Risk Assessment (75)	New York State ACMG (80)	UK Cancer Family Study Group (83)	Leiden WPHT (82)	Biomed 2 DPIBC (76)	Department of Defense FBOCRP (77)	Oxford Regional Genetics Service (78)	All-Wales Cancer Genetics Service (79)	National Breast Cancer Centre (81)	Review by Hampel et al. (84)
Women with a family history (but no personal history) of breast and/or ovarian cancer in maternal or paternal relatives as defined by ≥1 of the following:															
Breast cancer in ≥2 first- or second-degree relatives, with ≥2 cases diagnosed at age ≤49 y and with ≥1 of the relatives first-degree	X	X	X	X		X	X			X		X	X	X	X
Breast cancer in ≥3 first- or second-degree relatives, with ≥1 case diagnosed at age ≤49 y	X	X	X	X		X	X	X	X	X		X	X	X	X
Breast cancer in ≥1 first-degree relatives					X	X	X								
Breast cancer in ≥1 first- or second-degree relative, and ovarian cancer in ≥1 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 and testing procedures															
Counseling required before and/or after genetic test	X	X	X		X	X	X	X		X	X			X	
Affected relative tested first			X		X										
Informed consent required before testing	X	X	X	X	X										
Medical management recommendations provided for mutation carriers	X		X	X	X	X	X	X		X	X	X			
Additional recommendations in the guideline						X	X	X	X	X	X	X	X	X	X

* Adapted from Mouchawar et al., 2003 (74). ACMG = American College of Medical Genetics; DPIBC = Demonstration Programme on Inherited Breast Cancer; FBOCRP = Familial Breast/Ovarian Cancer Research Project; HMO = health maintenance organization; NCCN = National Comprehensive Cancer Network; UK = United Kingdom; WPHT = Working Party of Hereditary Tumors.
† Plans A, B, C, D: guidelines on genetic counseling referral for *BRCA* genes; plan E: counseling and testing guidelines for *BRCA* genes.

each trial and used in the meta-analysis. The overall estimates of RR were obtained by using a random-effects model (53).

We developed an outcomes table to determine the magnitude of potential benefits and adverse effects of testing for *BRCA* mutations in the general population based on best estimates 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% CI was based when available, or one that best approximated the point estimate and CI (Appendix 3, available at www.annals.org). The point estimates and 95% CIs of 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 3 risk groups, the total fell within the range for the general population (1 in 300 to 500) (41–44). Calculations assumed that women are cancer free at age 20 years, 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. We assumed that half of the mutations would be in *BRCA1* and half in *BRCA2*, and we did sensitivity analyses to determine whether this ratio (40/60, 50/50, 60/40) affects outcomes.

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with content experts, reviewed reports. The authors are responsible for the content of the manuscript and the decision to submit it for publication.

DATA SYNTHESIS

Do Risk Assessment and *BRCA* Mutation Testing Lead to a Reduction in the Incidence of Breast and Ovarian Cancer and Cause-Specific 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 reduces the incidence of breast and ovarian cancer and cause-specific or all-cause mortality.

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 clinically significant *BRCA* mutation in a woman without cancer or a known mutation in her family. A systematic review of studies of validated self-reported family histories addressed the accuracy of family cancer history information (54). Only 1 study determined the sensitivity and specificity of a family history of breast or ovarian cancer in first-degree relatives reported by individuals without cancer (55). In this study, a report of breast cancer in a first-degree relative had a sensitivity of 82% and a specificity of 91% (55). A report of ovarian cancer in a first-degree relative was less reliable, with a sensitivity of 50% and a specificity of 99% (55). Overall, accuracy was better in studies of first-degree rather than second-degree relatives (54).

Tools To Assess Risk for BRCA *Mutations*

Tools to assess risk for clinically significant *BRCA* mutations have been developed from data on previously tested women; however, no studies have examined their effectiveness in a screening population in a primary care setting (56). Much of the data used to develop the models are from women with existing cancer. Models with potential clinical applications (22–24, 57–72) are described in **Table 2**. Experts in the field consider mutation testing for women with a 10% or greater probability according to these estimations to be an appropriate threshold (73). Tools specifically designed for primary care that assess risk and guide referral have compared well with established models, such as BRCAPRO (67–70).

Referral Guidelines

Referral guidelines have been developed by health maintenance organizations (74), professional organizations (19, 20), cancer programs (75–79), state and national health programs (80–83), and investigators (84) to help primary care clinicians identify women at potentially increased risk for clinically significant *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 referral guidelines, and the effectiveness of this approach has not been evaluated.

What Are the Benefits of Genetic Counseling before Testing?

No studies describe cancer or mortality outcomes related to genetic counseling, although 10 randomized, controlled trials report psychological and behavioral outcomes (27–33, 85–87). 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 be generalizable to a screening population.

Results of 9 trials indicated either decreased measures of psychological distress (27, 30–33, 85–87) or no effect (29, 30, 32, 86) after genetic counseling. These include 5 trials reporting decreased breast cancer worry (27, 31–33, 86), 3 reporting decreased anxiety (27, 85, 87), and 1 reporting decreased depression (85). Findings are consistent with a meta-analysis of 12 randomized, controlled trials and prospective studies indicating that genetic counseling for breast cancer led to significant decreases in generalized anxiety, although the reduction in psychological distress was not significant (88). Five trials reported increased accuracy of perception of cancer risk among women who received genetic counseling (27, 29, 30, 33, 86, 87). One study showed less accurate risk perception after genetic counseling (85), and 1 had mixed results (30). Three studies examining the intention to participate in genetic testing after counseling reported inconsistent results (28, 31, 87).

Among Women with Family Histories Predicting an Average, Moderate, or High Risk for a Deleterious Mutation, How Well Does *BRCA* Mutation Testing Predict Risk for Breast and Ovarian Cancer?

Prevalence

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 the prevalence to be about 1 in 300 to 500 persons (41–44). For *BRCA1*, 1 model estimates a 0.12% prevalence rate (7). The prevalence among women with a strong family history of cancer is estimated to be 8.7% on the basis of 1 report from clinical referral populations that considered both *BRCA1* and *BRCA2* mutations together (21).

Additional prevalence estimates for individuals from referral populations with various levels of family history range from 3.4% (no breast cancer diagnosed in relatives < 50 years of age and no ovarian cancer) to 15.5% (breast cancer diagnosed in a relative < 50 years of age and ovarian cancer diagnosed at any age) (34). On the basis of these estimates, the prevalence of *BRCA1* and *BRCA2* mutations in women at average risk could be considered to be as high as 0.24%, moderate risk to be 0.24% to 3.4%, and high risk to be 8.7% and above. In the absence of direct measures, it can be assumed that half of the mutations would be in *BRCA1* and half would be in *BRCA2*.

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 (3, 41, 42, 89–92). Studies use a variety of research laboratory techniques, including a 2-step process in testing to detect clinically significant mutations that differ from the DNA sequencing available clinically. Use of these techniques may underestimate prevalence by one third (93). In addition, studies do not report the mutations' location on the gene, a factor that may influence penetrance (92, 94). Studies focus on women with existing breast and ovarian cancer and thereby introduce bias, since breast or ovarian cancer survivors may have different mutation frequencies than women with newly diagnosed cancer. Many studies estimated penetrance from families without the benefit of genetic testing of all family members (3, 41, 42, 89–92, 95–97). Such estimates are typically based on family members of women who have breast or ovarian cancer (probands) who probably have additional risk factors for breast cancer that affect penetrance (98).

To determine penetrance, we estimated values for the range of potential prevalence rates for each risk group (data not shown) (48). Estimates of prevalence rates of mutations for the general population for use in the outcomes table were assumed to be 0.12% for average-risk women, 1.5% for moderate-risk women, and 8.68% for high-risk women. This combination of prevalence rates reflects an overall population mutation rate of 1 in 397.

For breast cancer, 7 studies provide data on the probability of a *BRCA1* mutation if breast or ovarian cancer is present (24, 42, 43, 99–102), and 3 provide these data for a *BRCA2* mutation (42, 43, 101). *BRCA1* penetrance estimates to age 75 years are 68.6% (95% CI, 47.7% to 84.0%) in average-risk groups (102), 49.9% (CI, 27.5% to 72.3%) in moderate-risk groups (102), and 60.5% (CI, 52.3% to 68.2%) in high-risk groups (24, 42, 99, 102). For *BRCA2* penetrance, data are available only for the high-risk group (53.0% [CI, 42.2% to 63.5%]) (42).

For ovarian cancer, 6 studies provide data on the probability of a *BRCA1* mutation (57, 92, 99, 102–104) and 2 show data for a *BRCA2* mutation (92, 104). *BRCA1* penetrance estimates to age 75 years are 29.2% (CI, 20.3% to 40.1%) in average-risk groups (92, 104), 55.1% (CI, 48.4% to 61.5%) in moderate-risk groups (57, 92, 102, 103), and 26.1% (CI, 22.0% to 30.8%) in high-risk groups (99, 104). Respective estimates for *BRCA2* are 34.2% (CI, 22.9% to 47.6%) (92), 27.0% (CI, 17.3% to 39.6%) (92), and 6.4% (CI, 3.4% to 11.8%) (104). These penetrance estimates are similar to results of a combined analysis of 22 studies based on case series data from women unselected for cancer family history (89). Breast and ovarian cancer risk estimates to age 70 years for women who have a *BRCA1* mutation were 65% (CI, 44% to 78%) and 39% (CI, 18% to 54%), respectively; for *BRCA2* mutation carriers, breast and ovarian cancer risks were 45% (CI, 31% to 56%) and 11% (CI, 2% to 19%), respectively.

What Are the Adverse Effects of Risk Assessment, Genetic Counseling, and Testing?

Adverse effects include the potential for false-positive and false-negative results at each step of screening that lead to inappropriate reassurance or interventions. No studies directly address these issues. Fifty-seven studies describe another potential adverse effect, emotional distress. Of these, 9 studies met criteria for fair to good quality (105–113). One randomized, controlled trial (106) and 8 observational studies with before–after (113), case series (105), longitudinal (110), prospective cohort (107, 109, 111, 112), and noncomparative (108) 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, and follow-up periods ranged from immediate to 6 months. Only 2 studies distinguished between mutation carriers and noncarriers (109, 111). Studies were conducted in highly selected samples of women, and results may not be generalizable to a screening population.

Overall, more studies showed decreased (106, 107, 110, 111, 113) rather than increased (112) breast cancer worry or anxiety after risk assessment and testing, and 3 studies with depression outcomes had mixed results (110, 111, 114). Distress varied according to whether studies evaluated risk assessment, genetic testing, or both. In 4 studies that evaluated risk assessment (106, 108, 110, 113), most measures of breast cancer worry (106, 110), anxiety (110, 113), and depression (110) decreased, and only 1 measure of breast cancer worry increased (106, 108, 110, 113). When genetic testing was evaluated, breast cancer worry (105) and anxiety (112) increased, and results for depression were mixed (decreased for women who did not

Table 4. **Intensive Cancer Screening Studies of Women with Familial Breast Cancer Risk***

Study, Year (Reference)	Total Women, *n*	Inclusion Criteria	Mean Age at Entry (Range), *y*	Screening Methods	Mean Follow-up	Sensitivity, %
Warner et al., 2004 (124)	236	*BRCA* mutation carrier	46.6 (26.4–64.8)	Annual mammography + MRI + ultrasonography + CBE every 6 mo	100% round 1, 58% round 2, 36% round 3	95 (all methods combined)
Komenaka et al., 2004 (125)	13	*BRCA* mutation carrier	46 (32–59)	Annual mammography	NA	NA
Scheuer et al., 2002 (126)	165	*BRCA* mutation carrier	47.7 (24.1–79.0)	Annual mammography with or without MRI† + CBE every 3–6 mo	24.1 mo (range, 1.6–66.0 mo)	NA
Brekelmans et al., 2001 (115)	1198	Positive family history; RR > 2; includes 128 *BRCA* mutation carriers	38 (21–70)	Annual mammography with or without MRI† + CBE every 6 mo	36 mo	74
Chart and Franssen, 1997 (116)	1044	Positive family history or combination of other risk factors	39.5/42.7	Annual mammography + CBE every 6–12 mo	21.9 mo	91
Gui et al., 2001 (117)	1078	Positive family history; lifetime risk ≥ 17%	45 (26–66)	Annual mammography + CBE	NA	NA
Kollias et al., 1998 (118)	1371	Positive family history; lifetime risk > 11%	41 (18–49)	Biennial mammography + annual CBE	22 mo	66
Lai et al., 1998 (119)	2629	Relative of case-patient	NA (>35)	Annual mammography + CBE	NA	NA
Lalloo et al., 1998 (120)	1259	Positive family history; lifetime risk > 17%	39.1 (28–49)	Annual mammography	30 mo	87
Møller et al., 1996 (121)	1194	Positive family history	42.9	Annual mammography	1.8 y	NA
Saetersdal et al., 1996 (122)	537	Positive family history	42.5 (20–76)	Annual mammography + CBE	NA	NA
Tilanus-Linthorst et al., 2000 (123)	678	Lifetime risk >15%	42.9/43.3 (20–75)	Annual mammography with or without MRI† + CBE every 6–12 mo	3.3 y	92

* CBE = clinical breast examination; MRI = magnetic resonance imaging; NA = not available; RR = relative risk.
† In selected cases (dense breast tissue or *BRCA* carrier).

carry the mutation and increased for those who declined to obtain test results) (109).

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? What Are the Adverse Effects of Interventions?

Intensive Cancer Screening

No trials have studied the effectiveness of intensive cancer screening for *BRCA* mutation carriers in reducing mortality. **Table 4** describes available observational studies of breast cancer screening (115–126). Descriptive studies report increased risks for interval cancer (cancer occurring between mammograms) in *BRCA* mutation carriers with and without previous cancer undergoing annual mammographic screening (115, 125–127), implying that yearly mammograms may miss the highly proliferative types of cancer that are more common in *BRCA* mutation carriers (128–130).

To improve detection of early breast cancer in *BRCA* mutation carriers, 4 intensive cancer screening methods were compared in 236 women with known mutations (124). Women underwent 1 to 3 annual breast cancer screening examinations, including magnetic resonance imaging (MRI), mammography, and ultrasonography, with clinical breast examinations provided every 6 months. Magnetic resonance imaging was more sensitive for detecting breast cancer (sensitivity, 77%; specificity, 95.4%) than was mammography (sensitivity, 36%; specificity, 99.8%), ultrasonography (sensitivity, 33%; specificity, 96%), or clinical breast examination alone (sensitivity, 9%; specificity, 99.3%). Use of MRI, ultrasonography, and mammography together had a sensitivity of 95%. Only 1 case of interval cancer was reported, and 14% of women had biopsy findings that proved to be benign.

Data are limited on benefits of intensive screening strategies for ovarian cancer in *BRCA* mutation carriers. One study using transvaginal ultrasonography to screen 1610 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 (131).

We identified no studies describing the adverse effects of intensive cancer 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 (132), cost, harms resulting from false-positive findings and subsequent testing and biopsies, and false reassurance for women who

Table 5. **Randomized, Placebo-Controlled Trials of Chemoprevention for Breast Cancer***

Study, Year (Reference)	Participant Characteristics	Breast Cancer					
		Participants, *n*	Median Follow-up, *mo*	Outcome	Treatment Group, *n*	Placebo Group, *n*	Relative Risk (95% CI)
Tamoxifen, 20 mg/d							
International Breast Cancer Intervention Study, 2002 (133)	Increased breast cancer risk based on family history and other factors Mean age, 50.8 y; 40% using estrogen	Tamoxifen, 3573; placebo, 3566	50	Total	69	101	0.68 (0.50–0.92)
				Noninvasive	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, 1998 (134)	Increased breast cancer risk by Gail model Age ≥60 y, or risk factors; 39% < age 50 y; <10% using estrogen	Tamoxifen, 6576; placebo, 6599	55	Total	124	244	0.51 (0.41–0.63)†
				Noninvasive	35	69	0.50 (0.33–0.77)
				Invasive	89	175	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)†
Royal Marsden Hospital Trial, 1998 (135)	Family history of breast cancer developing at age <50 y or in ≥2 relatives Median age, 47 years; 26% using estrogen	Tamoxifen, 1238; placebo, 1233	70	Total	34	36	0.94 (0.59–1.49)†
				Noninvasive			NA
				Invasive			NA
				ER positive			NA
				ER negative			NA
				Deaths	4	1	3.98 (0.45–35.59)
Italian Tamoxifen Prevention Study, 1998 (136)	Women with hysterectomy Median age, 51 y; 14% using estrogen	Tamoxifen, 2700; placebo, 2708	46	Total	19	22	0.87 (0.47–1.60)†
				Noninvasive			NA
				Invasive			NA
				ER positive	8	10	0.80 (0.32–2.03)†
				ER negative			NA
				Deaths	0	0	NS
Raloxifene, 60 or 120 mg/d							
Multiple Outcomes of Raloxifene Evaluation, 1999 (137)	Postmenopausal women with osteoporosis Median age, 66.9 y; 10% receiving estrogen	Raloxifene, 5129; placebo, 2576	40	Total	22	32	0.35 (0.21–0.58)
				Noninvasive	7	5	0.70 (0.22–2.21)
				Invasive	13	27	0.24 (0.13–0.44)
				ER positive	4	20	0.10 (0.04–0.24)
				ER negative	7	4	0.88 (0.29–3.0)
				Deaths	1	0	NS

* DVT = deep venous thrombosis; ER = estrogen receptor; NA = not available; NS = not statistically significant; PE = pulmonary embolism; VTE = venous thromboembolic event.
† Calculated.

may have increased risks for developing cancer between periodic cancer screening tests.

Chemoprevention

Four randomized, placebo-controlled prevention trials of tamoxifen (133–136) and 1 trial of raloxifene (137) with breast cancer incidence and mortality outcomes have been published (**Table 5**), and a trial comparing these agents is in progress (138, 139). The raloxifene trial was not powered to measure breast cancer outcomes (137). None of the trials specifically evaluated chemoprevention for women with *BRCA* mutations, although a genomic analysis of women developing breast cancer in 1 tamoxifen trial has been published (140). No trials of chemoprevention for ovarian cancer have been published. Three tamoxifen trials had inclusion criteria based on assessment of risk for breast cancer (133–135). Two other trials did not assess participants for breast cancer risk, and women in these studies could have lower risks for breast cancer than the general population on the basis of eligibility criteria (136, 137, 141–143).

Combining all trials in a meta-analysis resulted in a relative risk for total breast cancer of 0.62 (CI, 0.46 to 0.83) (**Figure 2**). Results were similar when we included only the 3 tamoxifen trials that used family history of breast cancer as an inclusion criterion (133–135) and when we included only the 4 tamoxifen trials (133–136). Few deaths from breast cancer were reported in all the trials, and mortality did not differ between treatment and placebo groups. The relative risk (0.39 [CI, 0.20 to 0.79]) was further reduced for estrogen receptor–positive breast cancer (4 trials; 133, 134, 136, 137). This treatment effect could vary depending on the type of mutation because the proportion of estrogen receptor–positive tumors varies from 28% among women with *BRCA1* mutations to 63% among those with *BRCA2* mutations (140).

Several adverse effects were reported in the tamoxifen and raloxifene trials (**Table 5**). All trials indicated increased

Table 5—**Continued**

Adverse Effects			
Type	**Treatment Group, *n***	**Placebo Group, *n***	**Relative Risk (95% CI)**
VTE	43	17	2.5 (1.5–4.4)
PE	13	10	1.30 (0.57–2.96)†
DVT	24	5	4.79 (1.83–12.54)†
Stroke	13	11	1.18 (0.53–2.63)†
Endometrial cancer	11	5	2.2 (0.86–6.06)
All-cause death	25	11	2.27 (1.12–4.60)†
VTE	53	28	1.90 (1.20–3.00)†
PE	18	6	3.01 (1.15–9.27)
DVT	35	22	1.60 (0.91–2.86)
Stroke	38	24	1.59 (0.93–2.77)†
Endometrial cancer	36	15	2.53 (1.35–4.97)
All-cause death	57	71	0.81 (0.56–1.16)†
VTE	7	4	1.74 (0.51–5.94)†
PE	3	2	1.49 (0.25–8.93)†
DVT	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)†
VTE	7	4	1.76 (0.51–5.99)†
PE	1	1	1.00 (0.06–16.03)†
DVT	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)†
VTE	49	8	3.1 (1.5–6.2)
PE	17	3	2.85 (0.83–9.7)†
DVT	38	5	3.82 (1.50–9.69)†
Stroke			NA
Endometrial cancer	6	4	0.8 (0.2–2.7)
All-cause death			NA

risk (2.21 [CI, 1.63 to 2.98]) for thromboembolic events, including pulmonary embolism and deep venous thrombosis (5 trials; 133–137). Three trials reported that tamoxifen use was associated with an increased incidence of stroke (1.50 [CI, 1.01 to 2.24]) (133, 134, 136), 3 showed an increase in endometrial cancer (2.42 [CI, 1.46 to 4.03]) (133–135), and 1 showed an increase in all-cause death (2.27 [CI, 1.12 to 4.60]) (133). Trials reported significantly increased cataracts (134); hot flashes (133–135, 144); vaginal discharge, bleeding, and other gynecologic problems (133–135, 144); brittle nails (133); and mood changes (135), among other symptoms (137, 141, 144).

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 (145–147) as well as *BRCA* mutation carriers (148, 149) and an increase in breast cancer among women with family histories of breast cancer (150) and mutation carriers (151).

Prophylactic Surgery

No randomized, controlled trials of prophylactic surgery have been conducted, and cohort studies are methodologically limited (152). Bias may be introduced when treatment and comparison groups are not comparable, confounders are not considered (127, 153), and surgical procedures vary (154–160).

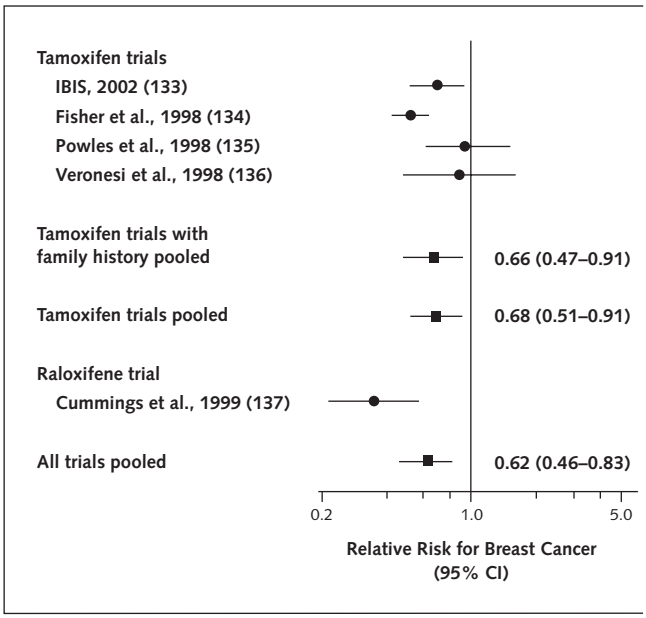
Four studies of prophylactic bilateral mastectomy in high-risk women have been published, including 2 retrospective cohort studies based on medical records at the Mayo Clinic (161, 162), a prospective cohort study of mutation carriers in the Netherlands (127), and a study of mutation carriers with prospective and retrospective cohort data from multiple centers in North America and Europe (163). Results were consistent, indicating an 85% to 100% risk reduction for breast cancer despite differences in study designs and comparison groups that included sisters (161), matched controls (163), a surveillance group (127), and penetrance models (162).

Little information exists about the complications of prophylactic mastectomy in healthy high-risk women, and data from patients with breast cancer 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 (164). Use of autologous tissue may eliminate the need for silicone implants but may result in higher complication rates (163).

Four studies of prophylactic oophorectomy met inclusion criteria: a retrospective study of families with breast and ovarian cancer (165), 2 retrospective cohort studies of mutation carriers undergoing oophorectomy compared with matched comparison groups in North America and Europe (166, 167), and a prospective cohort study of mutation carriers undergoing elective oophorectomy or surveillance (153). All studies reported reduced risks for ovarian and breast cancer with prophylactic oophorectomy, although numbers of cases were small and the CIs for the only prospective study crossed 1.0 for both outcomes (153). Overall, the risk reduction ranged from 85% to 100% for ovarian cancer and from 53% to 68% for breast cancer. One study found that oophorectomy after 50 years of age was not associated with substantial reduction in breast cancer risk (166), consistent with other studies of oophorectomy in the general population (168–171).

Surgical complications attributable to prophylactic oophorectomy are not well described and may vary with the type of surgical technique (172). Only 1 study of prophylactic oophorectomy in *BRCA* mutation carriers reported surgical complications (153). 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 (153). Premenopausal high-risk women are not only the most likely to benefit from prophylactic oophorectomy

Figure 2. **Relative risks for breast cancer in chemoprevention trials.**



Error bars represent 95% CIs. IBIS = International Breast Cancer Intervention Study.

but are also the most likely to experience additional side effects from surgery, including loss of fertility and induction of premature menopause.

Tubal ligation has been associated with a decreased risk for invasive epithelial ovarian cancer in observational studies (146, 173, 174). 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, after adjustment for oral contraceptive use, parity, history of breast cancer, and ethnic group (odds ratio, 0.39 [CI, 0.22 to 0.70]) (175). This protective effect was present only among *BRCA1* mutation carriers, although the number of *BRCA2* carriers was small in this study.

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 (176), only 16% to 20% rate it a favorable option (177, 178), and only 9% to 17% of women actually proceed with the surgery (176, 178, 179). Descriptive studies report improved concern about cancer after prophylactic surgeries (180–182) but also dissatisfaction with reconstruction (176), appearance (180), feelings of femininity (180), and sexual relationships (180), although several studies are inconclusive (183–186).

Genetic Risk Assessment Strategies

In the absence of direct evidence, we developed an outcomes table to determine the magnitude of potential benefits and adverse effects of screening for inherited breast and ovarian cancer susceptibility in the general population, stratified by average, moderate, and high risk for mutations according to family history as previously defined.

Results for the general population (**Table 6**) assume prevalence rates of mutations of 0.12% for average-risk, 1.5% for moderate-risk, and 8.68% for high-risk women and a 50/50 ratio of *BRCA1* and *BRCA2* mutations. This combination of prevalence rates reflects an overall population mutation rate of 1 in 397. The number needed to screen for benefit (NNS_B) to prevent 1 case of breast cancer in a hypothetical cohort of 100 000 women depends on which prevention therapy is chosen. For women with average risk, the NNS_B to prevent 1 case of breast cancer by age 75 years with chemoprevention is 12 862 (CI, 5425 to 64 048); for mastectomy, 11 049 (CI, 6243 to 27 037); and for oophorectomy, 4100 (CI, 1985 to 255 926). In comparison, trials of screening with mammography among women age 39 to 74 years indicate that approximately 550 to 3500 need to be invited for screening to prevent 1 death from breast cancer 13 to 20 years after randomization (187). Approximately 7072 (CI, 3610 to 584 750) women with average risk need to be screened to prevent 1 case of ovarian cancer by undergoing oophorectomy. The NNS_B for all treatment options, and for breast and ovarian cancer outcomes, decreases as risk for mutations increases (see outcomes for moderate- and high-risk women in **Table 6**). Under the assumptions of the outcomes table, if 100 000 women in the general population underwent testing for *BRCA* mutations, 16 cases of breast cancer would be prevented with mastectomy and 31 cases of ovarian cancer would be prevented with oophorectomy (**Figure 3**).

Table 6 also describes adverse effects. The number needed to treat with tamoxifen or raloxifene to cause a thromboembolic event each year is 1042 (CI, 641 to 2719), and the number needed to treat to cause a case of endometrial cancer each year is 2686 (CI, 1228 to 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 1 surgical complication; for oophorectomy, the number is 20. 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 years requires higher NNS_B values than those needed for cases that occur by age 75 years, and the prevalence ratios of *BRCA1* and *BRCA2* do not substantially influence the NNS_B (data not shown). In addition, if lower prevalence assumptions are used, the NNS_B increases (data not shown).

DISCUSSION

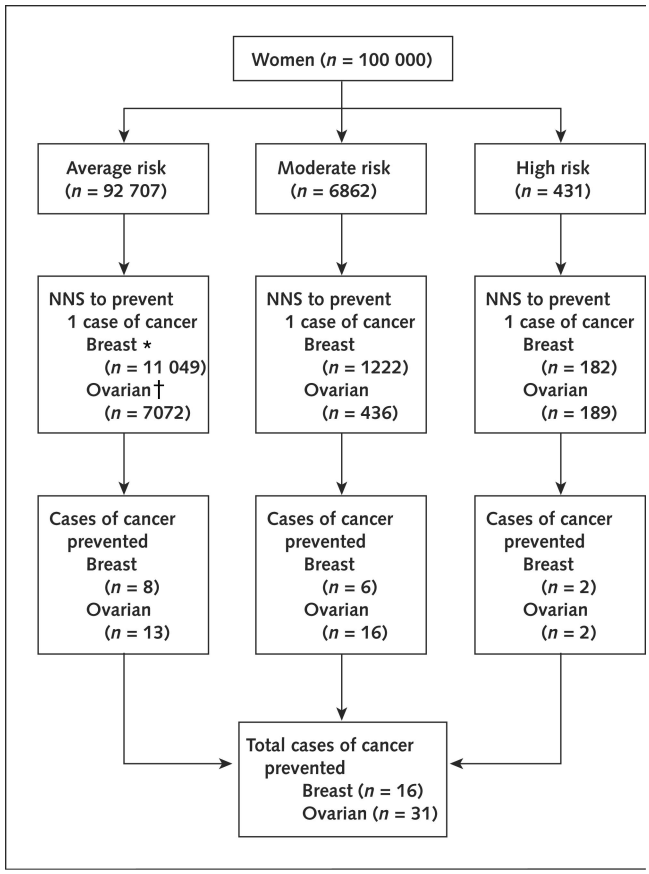
Little is known about *BRCA* mutations in the general population, and most data originate from studies of highly

Table 6. **Outcomes Table Summary***

Assumptions	Risk Level		
	Average	Moderate	High
Women screened, *n*	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 75 y, %			
Breast cancer			
BRCA1	68.6 (47.7–83.9)	49.9 (27.5–72.3)	60.5 (52.3–68.2)
BRCA2	No data†	No data†	53.0 (42.2–63.5)
Ovarian cancer			
BRCA1	29.2 (20.3–40.1)	55.1 (48.4–61.5)	26.1 (22.0–30.8)
BRCA2	34.2 (22.9–47.6)	27.0 (17.3–39.6)	6.4 (3.4–11.8)
Chemoprevention			
Risk reduction to prevent breast cancer‡	0.38 (0.17–0.54)	0.38 (0.17–0.54)	0.38 (0.17–0.54)
Risk for thromboembolic events, *% per year*‡	0.096 (0.036–0.156)	0.096 (0.036–0.156)	0.096 (0.036–0.156)
Risk for endometrial cancer, *% per year*‡	0.036 (0.00177–0.0709)	0.036 (0.00177–0.0709)	0.036 (0.00177–0.0709)
Proportion of candidates choosing this option, *estimated %*§	5–50	5–50	5–50
Mastectomy			
Risk reduction to prevent breast cancer in mutation carriers	0.91 (0.64–1.00)	0.91 (0.64–1.00)	0.91 (0.64–1.00)
Risk for complications, *% overall*	21	21	21
Proportion of candidates choosing this option, *estimated %*§	5–20	5–20	5–20
Oophorectomy			
Risk reduction to prevent breast cancer in mutation carriers	0.68 (0.01–0.92)	0.68 (0.01–0.92)	0.68 (0.01–0.92)
Risk reduction to prevent ovarian cancer in mutation carriers	0.85 (0.01–0.99)	0.85 (0.01–0.99)	0.85 (0.01–0.99)
Risk for complications, *% overall*	5	5	5
Proportion of candidates choosing this option, *estimated %*§	25–75	25–75	25–75
Outcomes—benefits to age 75 y			
Breast cancer cases expected among mutation carriers if not undergoing treatment, *n*	82 (65–96)	748 (508–989)	4925 (4341–5493)
Breast cancer cases prevented among mutation carriers using chemoprevention, *n*	7.8 (1.6–18.4)	71 (14–177)	474 (96–1100)
NNS_B to prevent 1 case of breast cancer using chemoprevention	12 862 (5425–64 048)	1419 (567–7237)	211 (91–1043)
NNT_B with chemoprevention 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)
Breast cancer cases prevented among mutation carriers undergoing mastectomy, *n*	9.1 (3.7–16.0)	82 (32–157)	550 (230–943)
NNS_B to prevent 1 case of breast cancer using mastectomy	11 049 (6243–27 037)	1222 (639–3142)	182 (107–435)
NNT_B 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)
Breast cancer cases prevented among mutation carriers if undergoing oophorectomy, *n*	24.4 (0.39–50.4)	222 (3.5–486)	1483 (24–2990)
NNS_B to prevent 1 case of breast cancer using oophorectomy	4100 (1985–255 926)	452 (206–28 242)	68 (34–4204)
NNT_B 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)
Ovarian cancer cases expected among mutation carriers if not undergoing treatment, *n*	38 (29–48)	616 (527–721)	1422 (1186–1718)
Ovarian cancer cases prevented among mutation carriers undergoing oophorectomy, *n*	14.1 (0.17–27.7)	230 (2.8–431)	530 (6.4–1006)
NNS_B to prevent 1 case of ovarian cancer using oophorectomy	7072 (3610–584 750)	436 (232–35 652)	189 (100–15 565)
NNT_B 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)
Outcomes—adverse effects			
Women using chemoprevention, *n*	33 (7.3–59)	412 (92–733)	2386 (532–4242)
Cases of thrombotic events due to chemoprevention per year, *n*‡	0.032 (0.005–0.073)	0.40 (0.068–0.91)	2.29 (0.40–5.28)
NNT_B with chemoprevention to cause 1 thrombotic event per year	1042 (641–2719)	1042 (641–2719)	1042 (641–2719)
Cases of endometrial cancer due to chemoprevention per year, *n*‡	0.012 (0.00039–0.032)	0.15 (0.005–0.40)	0.87 (0.029–2.32)
NNT_B with chemoprevention to cause 1 case of endometrial cancer per year	2686 (1228–15 726)	2686 (1228–15 726)	2686 (1228–15 726)
Women undergoing mastectomy, *n*	15.0 (6.4–23.6)	188 (80.6–294)	1085 (467–1703)
Women with complications from mastectomy, *n*	3.2 (1.4–4.9)	39.4 (16.9–61.8)	228 (98–358)
NNT_B with mastectomy to cause 1 complication	5	5	5
Women undergoing oophorectomy, *n*	60 (32–89)	750 (394–1106)	4342 (2279–6401)
Women with complications from oophorectomy, *n*	3.0 (1.6–4.4)	37.5 (19.7–55.3)	217 (114–320)
NNT_B with oophorectomy to cause 1 complication	20	20	20

* NNS_B = number needed to screen for benefit; NNT_B = number needed to treat for benefit.
† Assumed to be equal to penetrance for *BRCA1* in table.
‡ Based on trials of tamoxifen and raloxifene enrolling women with unknown mutation status; endometrial cancer estimates for tamoxifen only.
§ Proportion choosing this option is not known but is assumed to have a uniform distribution across an estimated range.

Figure 3. **Yield of testing for *BRCA* mutations in a hypothetical population based on assumptions in Table 6.**



NNS = number needed to screen. *Based on estimates for mastectomy. †Based on estimates for oophorectomy.

selected women with existing cancer or strong family histories of cancer. Tools assessing individual risks for mutations and referral guidelines have been developed, but their accuracy, effectiveness, and adverse effects in primary care settings are unknown. Risk assessment tools are recommended as an adjuvant to genetic counseling (63). 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. 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. However, long-term effects are unknown, studies did not evaluate psychological aspects of medical outcomes, and little is known about the impact of testing on family members.

Currently available prevention interventions include intensive cancer screening, chemoprevention, and prophylactic mastectomy and oophorectomy. Intensive cancer screening studies are descriptive and inconclusive, and recent studies suggest improved breast cancer detection using MRI. A meta-analysis of randomized, controlled trials of tamoxifen and raloxifene indicates significant risk reduction for breast cancer in women with varying levels of family history risk for breast cancer. Results also show significantly increased risks for thromboembolic events and, for tamoxifen, increased endometrial cancer. Observational studies of prophylactic surgeries report reduced risks for breast and ovarian cancer in mutation carriers.

Estimating mutation prevalence and penetrance and stratifying by average-, moderate-, and high-risk groups based on family history can be used to determine the yield of screening in populations that would present to primary care clinicians. Applying these estimates to an outcomes table that considers treatment effects provides calculations of benefits and adverse effects for main outcomes. The NNS_B to prevent 1 case of breast or ovarian cancer is high among low-risk women and decreases as risk increases. Adverse effects also increase as more women are subjected to therapies.

Although the outcomes table estimates can be useful, caution is necessary in extrapolating too far from the primary data. The quality and generalizability of studies vary and may not support the assumptions. Only limited data describe the range of risk associated with *BRCA* mutations, genetic heterogeneity, and moderating factors outside the gene. Data are 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 testing for *BRCA* mutations reduces cause-specific or all-cause mortality and improves quality of life. The adverse effects associated with receiving a false-negative test result (12% to 15% with DNA sequencing), or a result indicating mutations of unknown significance (approximately 13%), are not known. Nonquantitative measures, such as ethical, legal, and social implications, are not factored into the outcomes table. Treatment effects are influenced by several factors, including age at which treatment is initiated (166), type of mutation (89, 140), adherence, and cost. It is not known how these differences influence patient decision making.

To determine the appropriateness of risk assessment and testing for *BRCA* mutations in primary care, more information is needed about the impact of screening in the general population. 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 these services should be provided, and what skills are needed are unresolved questions. What happens after patients are identified as high risk in clinical settings and the consequences of genetic testing on individuals and their relatives are unknown. Well-designed investigations using standardized measures and enrolling participants who reflect the general population, including minority women, are needed. An expanded database or registry of patients coun-

seled and tested for *BRCA* mutations would provide useful information about predictors of cancer, response to interventions, and other modifying factors. Current research resources that may help address some of these questions include the National Cancer Institute–funded Cancer Genetics Network (52) and Breast and Ovarian Cancer Family Registries (188). Additional research on interventions is needed, including chemoprevention trials of mutation carriers, evaluation of the effect of age at intervention, measurement of long-term outcomes, and factors related to acceptance of preventive interventions. This information could improve patient decision making and lead to better health outcomes.

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Appendix 1

Diagnostic Accuracy Studies

Criteria

1. Screening test relevant, available for primary care, adequately described.
2. Credible reference standard, performed regardless of test results.
3. Reference standard interpreted independently of screening test.
4. Indeterminate results handled in a reasonable manner.
5. Spectrum of patients included in study.
6. Sample size.
7. 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; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (>100) broad-spectrum patients with and without disease.

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

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

Randomized, Controlled Trials and Cohort Studies

Criteria

1. Initial assembly of comparable groups: randomized, controlled trials—adequate randomization, including concealment and statement of 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.
2. Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination).
3. Important differential loss to follow-up or overall high loss to follow-up.
4. Measurements: equal, reliable, and valid (includes masking of outcome assessment).
5. Clear definition of interventions.
6. Important outcomes considered.
7. Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for randomized, controlled trials.

Definition of Ratings Based on Above Criteria

Good: Meets all criteria—comparable groups are assembled initially and maintained throughout the study (follow-up ≥80%), 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 as to 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 failure to mask outcome assessment), and key confounders are given little or no attention.

Case–Control Studies

Criteria

1. Accurate ascertainment of cases.
2. Nonbiased selection of case-patients and controls, with exclusion criteria applied equally to both.
3. Response rate.
4. Diagnostic testing procedures applied equally to each group.
5. Measurement of exposure accurate and applied equally to each group.
6. Appropriate attention to potential confounding variable.

Definition of Ratings Based on Above Criteria

Good: Appropriate ascertainment of cases and nonbiased selection of case-patients and controls, exclusion criteria applied equally to case-patients and controls, response rate of 80% or greater, diagnostic procedures and measurements accurate and applied equally to case-patients 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% or attention to some but not all important confounding variables.

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

Appendix 2

The meta-analysis of penetrance was based on the Bayes theorem and stratified by cancer type (breast or ovarian), risk group (average, moderate, and high), and age. 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 the Bayes theorem, penetrance is given by:

$$P(D^+|G) = \frac{P(G|D^+)\,P(D^+)}{P(G)}$$

$$= \frac{P(G|D^+)\,P(D^+)}{P(G|D^+)\,P(D^+) + P(G|D^-)\,P(D^-)} \quad (1)$$

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 using DevCan software (52) 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 for 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 are estimated from different studies in a meta-analysis by using a random-effects model (53).

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

$$P(D^+|G) = \frac{1}{1 + \dfrac{P(G|D^-)\,P(D^-)}{P(G|D^+)\,P(D^+)}} \quad (2)$$

then,

$$\text{logit}(P(D^+|G)) = \log\left(\frac{P(G|D^+)\,P(D^+)}{P(G|D^-)\,P(D^-)}\right).$$

Assuming that $P(G|D^+)$ and $P(G|D^-)$ are independent with each other, standard calculation using delta-method shows:

$$\text{var}(\text{logit}(P(D^+|G))) = \frac{\text{var}(P(G|D^+))}{P(G|D^+)^2} + \frac{\text{var}(P(G|D^-))}{P(G|D^-)^2} \quad (3)$$

Usually, $\text{logit}(P(D^+|G))$ is assumed to be normally distributed and the 95% CI of $\text{logit}(P(D^+|G))$ is given as

$$\left(\text{logit}(P(D^+|G)) \pm Z_{0.975} \times \sqrt{\text{var}(\text{logit}(P(D^+|G))}\right)$$

where $Z_{0.975}$ is the 97.5% quantile of the standard normal distribution. The 95% CI 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 with which to estimate $P(G|D^-)$, and we used the best point estimates available in the literature. However, SEs associated with the point estimates are usually not available. Under such conditions, the second part of equation 3 on the right side would be zero, and the 95% CI for the penetrance would be underestimated.

Equation 1 provides the formula to calculate penetrance in general. It is easy to extend equation 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, denoted by D_x^+, in equation (1), which gives

$$P(D_x^+|G) = \frac{P(G|D_x^+)\,P(D_x^+)}{P(G|D_x^+)\,P(D_x^+) + P(G(D_x^+)^-)(1 - P(D_x^+))} \quad (4)$$

In this analysis, we assume

$$P(G|(D^+\text{by age } x)^-) \approx P(G|D^-).$$

In our analysis, we calculated penetrance of breast cancer to ages 40 and 75 years and ovarian cancer to ages 50 and 75 years to be consistent with how age was considered by the studies.

For penetrance of *BRCA* mutations when a positive family history is present,

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

We conducted a sensitivity analysis in the average-risk groups by calculating penetrance 2 ways: including and excluding studies of women with family history of breast or ovarian cancer. Calculation of 95% CI for penetrance in equations 4 and 5 is similar to that described above, with appropriate substitution of terms.

Appendix 3

Several estimates were used to develop the outcomes table. This appendix provides 2 examples of specification of sampling distributions for these estimates.

1. Sampling Distribution for Penetrance $P(D^+|G)$:

The estimate of $P(D^+|G)$ is obtained from our analysis. We assumed that $\text{logit}(P(D^+|G))$, denoted as $\text{logit}(P)$ for concise notation, is approximately normally distributed and estimated $\text{logit}(P)$ and its variance from data available in the literature. Estimate of $P(D^+|G)$ and its CI is obtained by transforming $\text{logit}(P)$ and its CI (see Appendix 2 for more information).

In Monte Carlo simulation, random samples for the estimate of $P(D^+|G)$ are obtained as follows. First, random samples of $\text{logit}(P)$ are drawn from the following normal distribution:

$$N\left(\widehat{\text{logit}}(P), \widehat{\text{var}}\left(\widehat{\text{logit}}(P)\right)\right)$$

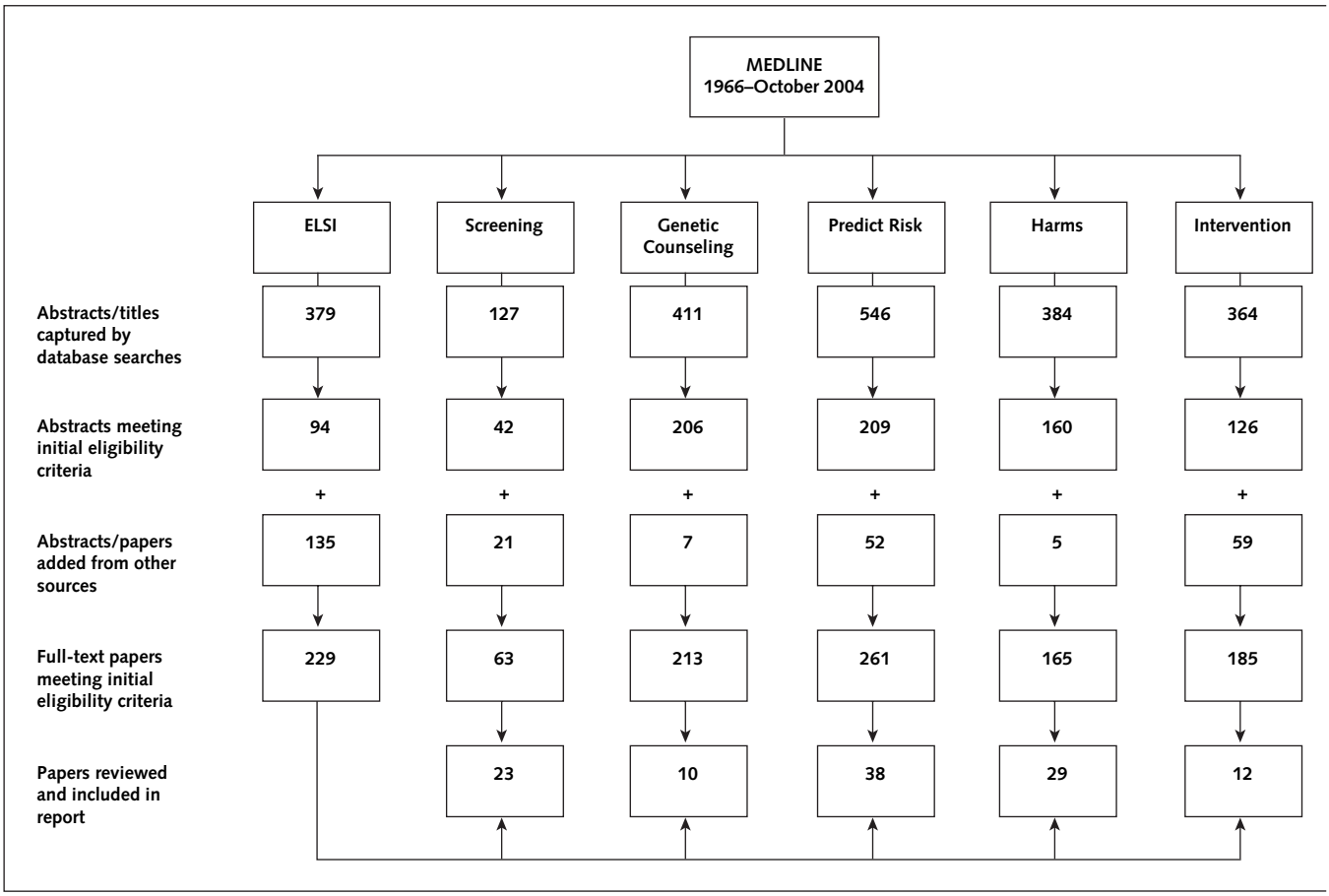
where $\widehat{\text{logit}}(P)$ and $\widehat{\text{var}}(\widehat{\text{logit}}(P))$ are estimated values for $\text{logit}(P)$ and its variance. Then, by transformation, random samples for estimates of $P(D^+|G)$ are obtained as:

$$P(D|G^+) = \frac{\exp(\text{logit}(P))}{1 + \exp(\text{logit}(P))}$$

2. Sampling Distribution for Relative Risk

When developing the outcomes table, the estimates of relative risk (RR) are obtained from published studies. Usually, the point estimate $\widehat{RR}$ and its 95% CI (RR_L, RR_U) are reported.

Appendix Figure. **Yield of literature search and review.**



ELSI = ethical, legal, and social implications.

Since ln(RR) is usually assumed to be approximately normally distributed, we calculate

$$\hat{se}(\ln(\widehat{RR})) = (\ln(RR_U) - \ln(RR_L))/(2^{*}Z_{0.975})$$

and,

$$\widehat{\mathrm{var}}(\ln(\widehat{RR})) = (\hat{se}(\ln(\widehat{RR})))^2$$

where $Z_{0.975}$ is the 97.5% quantile of the standard normal distribution. Random samples of RR are obtained by first drawing random samples of ln(RR) from $N(\ln(\widehat{RR}), \widehat{\mathrm{var}}(\ln(\widehat{RR}))$ and then transforming to RR by taking exponentiation.

If we recalculate the 95% CI for RR by using

$$\hat{se}(\ln(\widehat{RR})),$$

the resulting CI usually agrees very well with the reported (RR_L, RR_U).

Appendix Table. **Inclusion and Exclusion Criteria according to Key Question***

Question	Criteria
KQ 1, 2a, 3 (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 participants Overview, meta-analysis, or review with relevant information Cost
Exclude	Not applicable to U.S. primary care setting Study limitations (small number of participants, noncomparative, single case report) No data (commentary, letter, opinion) Information not relevant (dated, off-topic)
KQ 1, 2b, 3 (genetic counseling)	
Include	Randomized, controlled trial Comparative study (cohort, case–control, or observational study) with ≥50 participants Overview, meta-analysis, or review with relevant information Practice standards or guidelines Cost
Exclude	Not applicable to U.S. primary care setting Study limitations (small number of participants, noncomparative, single case report) No data (commentary, letter, opinion) Information not relevant (dated, off-topic)
KQ 1, 2c, 3 (genetic testing)	
Include	Genetic testing for heritable clinically significant *BRCA1* and/or *BRCA2* mutations (excludes studies of tumor tissue only) Participants from United States, Canada, United Kingdom, Australia, or Israel ≥50 participants
Exclude	Risk model only No primary data included (include meta-analysis) Not *BRCA1* or *BRCA2* Not breast or ovarian cancer No genetic testing Only second cancer at same site (risk for second, contralateral cancer) Basic science only (studies of gene function or gene expression) Tumor tissue only Linkage and/or segregation analysis (i.e., no testing for *BRCA1* or *BRCA2* mutations)
KQ 4 and KQ 5 (interventions and adverse effects)	
Include	Randomized, controlled trial Comparative study (cohort, case–control, or observational study) with ≥50 participants 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 number of participants, noncomparative, single case report) No data (commentary, letter, opinion) Information not relevant (dated, off-topic)

* KQ = key question.