Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: evidence synthethis

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CRD summary
The review evaluated screening for inherited breast or ovarian cancer susceptibility in the U.S. general population. The review concluded that the evidence base was limited, and that most studies have been conducted in highly selected populations. This conclusion is likely to be reliable, although some aspects of the review did not meet DARE criteria and could not be commented on.

Authors' objectives
To determine the 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. The following questions were addressed using an analytical framework:

Q1) Does 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?

Q2) What are the ethical, legal and social implications of genetic screening for breast and ovarian cancer susceptibility?

Q3a) How well does risk assessment for cancer susceptibility by a clinician in a primary care setting select candidates for BRCA mutation testing?

Q3b) What are the benefits of genetic counselling prior to testing?

Q3c) Among women with family histories predicting an average, moderate, or high risk for a deleterious mutation, how well does BRCA mutation testing predict risk of breast and ovarian cancer?

Q4) What are the adverse effects of risk assessment, counselling and testing?

Q5) What 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?

Q6) What are the adverse effects of interventions?

Questions 1, 3b, 4, 5 and 6 meet DARE inclusion criteria and are presented herein.

Searching
MEDLINE (from 1966 to 2004) and The Cochrane Library were searched for articles published in English. Search strategies were developed and reported for each review question. Reference lists of relevant studies, reviews, editorials and websites were also searched. Experts were contacted for knowledge of additional studies.

Study selection

Study designs of evaluations included in the review
Overviews, meta-analyses, randomised controlled trials (RCTs), and comparative studies (cohort, case-controls or observational studies) with more than 50 participants were eligible for inclusion for Q5 and Q6. RCTs only were eligible for inclusion for Q3b. No explicit inclusion criteria for study design were reported for Q1 or Q4. Descriptive studies were also included if relevant to the key questions.

Specific interventions included in the review
Studies of genetic risk assessment and BRCA mutation testing for breast and ovarian cancer were eligible for inclusion. Tools for risk assessment included logistic regression and Bayesian models and risk scoring systems. Guidelines for referral for genetic counselling and testing were also included. In the included studies for Q3b, genetic counselling was
provided by a genetic counsellor, mental health counsellor, nurse educator or computer-based decision aid. Studies of intensive screening (surveillance), chemoprevention and prophylactic surgery were eligible for inclusion for Q5 and Q6. No additional inclusion criteria were reported for Q1 and Q4. The studies had to be applicable to the U.S. setting and any studies reporting 'dated' or 'off-topic' data were excluded.

Reference standard test against which the new test was compared
The review did not include any diagnostic accuracy studies that compared the performance of the index test with a reference standard of diagnosis.

Participants included in the review
Studies of asymptomatic women were eligible for inclusion. Studies of women with current or past breast or ovarian cancer were excluded. Most of the included studies of BRCA mutations were performed in highly selected samples of women considered to be at high risk.

Outcomes assessed in the review
The studies had to report primary data relevant to the key question to be eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Each study was assigned a quality rating of 'good', 'fair' or 'poor', based on the U.S. Preventive Services Task Force criteria. Separate criteria were used for diagnostic accuracy studies, RCTs and cohort studies, and for case-control studies. Only studies rated as fair or good were included. Further details were given in the report. Two reviewers independently rated the quality of the included studies. Any disagreements were resolved by re-evaluation and by consulting a third reviewer.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted into evidence tables to provide a descriptive and/or statistical summary as appropriate to each key question.

Methods of synthesis

How were the studies combined?
The results of studies addressing each key question were presented in evidence tables and summarised using descriptive and/or statistical methods. Studies of chemoprevention were combined using a random-effects meta-analysis. A pooled relative risk with 95% confidence intervals was calculated overall and separately for each type of drug. An outcomes table was developed to determine the potential magnitude of benefits and harms of screening for BRCA mutations in the general population, based on evidence derived from each of the key questions. This was used to calculate the benefits and harms (the number-needed-to-screen, number-needed-to-treat and risk of adverse events) in the general population, stratified by risk for mutation (average, moderate or high) as determined by family history.

How were differences between studies investigated?
For chemoprevention studies, separate analyses were performed for studies that used a family history of breast cancer as an inclusion criterion, and for tamoxifen only studies. A separate analysis was also undertaken for studies of oestrogen-receptor-positive breast cancer. In the outcomes table, sensitivity analyses were performed for each of the assumptions.

Results of the review
For Q3b, 10 RCTs evaluated genetic counselling.

For Q4, four studies evaluated risk assessment, two studies evaluated risk assessment and testing, and three studies evaluated testing only.
For Q5, five studies evaluated chemoprevention, four studies evaluated prophylactic bilateral mastectomy and four studies evaluated prophylactic oophorectomy. For Q6, five studies reported adverse events of chemoprevention, and observational and descriptive data were used for adverse events of prophylactic surgery.

In terms of methodological quality, overall, most of the studies were rated ‘fair’ quality and others were rated ‘good’.

Q3b. Does 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?

No studies were identified.

Q4. What are the adverse effects of risk assessment, genetic counselling and testing?

No studies evaluated cancer or mortality outcomes in relation to genetic counselling. Overall, more studies reported decreased rather than increased breast cancer worry or anxiety after risk assessment and testing, while studies with depression as an outcome had mixed results. The studies were conducted in highly selected populations who were mainly white and had a high socioeconomic status.

Q5 and Q6. How well do interventions reduce the incidence and mortality of breast and ovarian cancer in women identified as high-risk by history and/or positive genetic test results, and what are the adverse effects of interventions?

No trials evaluating the effectiveness of intensive cancer screening for BRCA mutation carriers in reducing mortality were identified. No studies reporting the adverse events of intensive screening for breast or ovarian cancer were identified.

For chemoprevention, four RCTs evaluating tamoxifen and one evaluating raloxifene were identified. None of the included studies specifically evaluated chemoprevention for women with BRCA mutations. Chemoprevention was associated with a significant reduction in breast cancer (RR 0.62, 95% CI 0.46 to 0.83). The results were similar for studies of tamoxifen that included women with a family history of breast cancer (three studies). The risk of oestrogen-receptor-positive breast cancer was also significantly reduced (RR 0.39, 95% CI 0.20 to 0.79).

Five RCTs found that chemoprevention was associated with an increased risk of thromboembolic events (RR 2.21, 95% CI 1.63 to 2.98), three found an increased risk of stroke (RR 1.50, 95% CI 1.01 to 2.24), and three found an increased risk of endometrial cancer (RR 2.42, 95% CI 1.46 to 4.03). Other commonly reported adverse events were cataracts, hot flashes and gynaecological problems.

No RCTs on the use of oral contraceptives to prevent breast or ovarian cancer were identified. Observation studies suggested that oral contraception was associated with reduced ovarian cancer in the general population (three studies) and in BRCA carriers (two studies), but an increased risk of breast cancer among those with a family history (one study) and mutation carriers (one study).

No RCTs on the use of prophylactic surgery were identified. Four observational studies of prophylactic bilateral mastectomy in high-risk women found a risk reduction of breast cancer ranging from 85 to 100%. One additional study found a 21% risk of complications in high-risk women who had a prophylactic mastectomy with immediate reconstruction. Four observational studies of prophylactic oophorectomy in high-risk women found a risk reduction ranging from 85 to 100% for ovarian cancer and from 53 to 68% for breast cancer. One study of prophylactic oophorectomy in carriers of BRCA mutations found a complication risk of 5%. Four observational studies found a decreased risk for invasive epithelial ovarian cancer.

Descriptive studies of the psychological harms of prophylactic mastectomy or oophorectomy in high-risk women found mixed results; some suggested that cancer distress improved, but self-esteem, body image and some other outcomes could be adversely affected.

**Authors’ conclusions**

Based on all the evidence presented in the review, the authors concluded that a primary care approach to screening for inherited breast or ovarian cancer susceptibility has yet to be evaluated. The benefits and harms in the general
population need to be determined.

**CRD commentary**
The review addressed a series of clear questions. The inclusion criteria were broad and attempted to include participants who would be representative of the US population. However, it was unclear how this was defined or assessed when determining the eligibility of studies for inclusion. The search was limited to two named databases, although attempts were made to identify unpublished studies or studies published elsewhere. Methods used to minimise reviewer bias and error in the study selection and data abstraction processes were not reported, whereas the validity assessment was conducted in duplicate. Inclusion was restricted to studies meeting a minimum quality rating, although in some cases descriptive data were also reported.

Adequate details of the studies used for each key question were reported. The methods used to summarise the results of the key questions were appropriate. The authors also considered the limitations of the review in terms of generalisability and assumptions made in the outcomes table.

Overall, the authors’ conclusions are likely to be reliable, although it was not possible to comment on the reliability of the conclusions for those key questions that did not meet the inclusion criteria for DARE.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that to determine the appropriateness of risk assessment and testing for BRCA mutations in primary care, studies to assess the impact of screening in the general population are needed. Specific areas of research include access to testing, effectiveness of screening approaches, use of system reports and patient acceptance. Research needs to be conducted using standardised measures in populations that are representative of the general population. Further research into interventions is needed to improve patient decision-making.

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**Bibliographic details**

- Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: a systematic review to update the U.S. Preventive Services Task Force Recommendation

**Original Paper URL**

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Breast Neoplasms /genetics /prevention & control; Female; Genes, BRCA1; Genes, BRCA2; Genetic Counseling; Genetic Predisposition to Disease; Medical History Taking; Mutation; Ovarian Neoplasms /genetics /prevention & control; Risk Assessment; Risk Factors
This is a systematic review that meets the criteria for inclusion on DARE. It is linked to: