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Risk reduction and survival benefit of prophylactic surgery in *BRCA* mutation carriers, a systematic review

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Abstract

BACKGROUND: Mutations in *BRCA1* or *BRCA2* genes results in an elevated risk for developing both breast and ovarian cancers over the lifetime of affected carriers. General surgeons may be faced with questions about surgical risk reduction and survival benefit of prophylactic surgery.

METHODS: A systematic literature review was performed using the electronic databases PubMed, OVID MEDLINE, and Scopus comparing prophylactic surgery vs observation with respect to breast and ovarian cancer risk reduction and mortality in *BRCA* mutation carriers.

RESULTS: Bilateral risk-reducing mastectomy provides a 90% to 95% risk reduction in *BRCA* mutation carriers, although the data do not demonstrate improved mortality. The reduction in ovarian and breast cancer risks using risk-reducing bilateral salpingo-oophorectomy has translated to improvement in survival.

CONCLUSIONS: Clinical management of patients at increased risk for breast cancer requires consideration of risk, patient preference, and quality of life.

Breast cancer is the most commonly diagnosed cancer in women in the United States with approximately 232,340 new cases a year.[1] Hereditary breast cancer accounts for only 5% to 10% of all cases of breast cancer.[2] Hereditary breast and ovarian cancer syndrome (HBOC) is associated with mutations in the breast cancer 1 gene (*BRCA1*) and breast cancer 2 gene (*BRCA2*). *BRCA1* and *BRCA2* account for approximately 40% to 50% of all HBOC. The genes *TP53*, *PTEN*, *PALB2*, *CHEK2*, and *STK11* are also estimated to explain less than 10% of HBOC cases.[2] The rest are because of unknown genetic variants or a small number of very rare, known mutations in other genes.[2–8] Because of the lack of evidence regarding surgical risk reduction

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treatments in patients with other mutations, this systematic review is focused on the evidence for surgical risk reduction strategies for *BRCA1* and *BRCA2* mutation carriers.

Once an individual has been determined to be a carrier of a *BRCA* mutation, discussions about cancer surveillance and prevention should be initiated. Patients should undergo regular clinical breast examination and imaging of the breasts with annual magnetic resonance imaging (MRIs) starting at age 25 and annual mammograms at 30.[9] A recent study reported that annual MRI in women with *BRCA* mutations decreases the risk of stage II to IV breast cancer at 6 years to 1.9% compared with 6.6% with conventional screening ($P = .02$).[10]

Methods for early detection of ovarian cancer are less reliable. The National Comprehensive Cancer Network guidelines recommend risk-reducing bilateral salpingo-oophorectomy (RRBSO) in *BRCA* mutation patients between the ages of 35 and 40 years. If a patient declines RRBSO, transvaginal ultrasound and CA-125 testing could be considered based on clinical judgment.[9] Such patients should be counseled that ovarian cancer screening has not yet been shown to increase early detection of disease or reduce mortality.[11]

With increasing awareness of *BRCA1* and *BRCA2* gene mutations and genetic testing, general surgeons are often faced with the surgical management of patients who harbor these mutations. The primary literature is limited on the risk reduction and mortality benefit that prophylactic surgery provides to this patient population. Using a systematic review, our study aims to examine the current surgical management strategies for the reduction of breast and ovarian cancer risk and cancer mortality in patients with *BRCA* mutations.

Methods

Search strategy

The preferred reporting items for systematic reviews and meta-analyses statement was followed to perform the systematic review that included trials without any restrictions on publication date. The last search was carried out on January 16, 2016. A review of surgical management strategies for *BRCA* mutation carriers was performed by searching the electronic databases PubMed, OVID MEDLINE, and Scopus. The terms "risk reduction," "risk reducing," "prophylactic," "BRCA1," "BRCA2," "BRCA," and "mastectomy" were used for the first search and the terms "risk reduction," "risk reducing," "prophylactic," "BRCA1," "BRCA2," "BRCA," and "oophorectomy" were used for the second search. Only those publications in English were included. Review articles, case reports, commentaries, published conference abstracts, and letters were excluded. Additional articles were found through review of references and tables.

Two independent reviewers (K.L. and A.K.) selected the studies based on title and abstract and if information regarding the premise of the study could not be determined, a full-text version was reviewed. Studies were selected if the cohort of patients included those positive for *BRCA* mutations who underwent surgery for prophylactic reasons. Many studies in this patient population are collaborations of co-operative groups or multiple centers. To prevent inclusion of redundant data, if multiple reports were published from a single group/collaboration, only the most recent publication with the longest follow-up was included. A meta-analysis was not performed because of the heterogeneity of the study end points (overall survival, breast and ovarian cancer–specific mortality, cancer occurrence after prophylactic surgery).

Results

Our literature search for prophylactic or risk-reducing mastectomy in *BRCA* patients identified 1,902 articles through PubMed, OVID MEDLINE, and Scopus. After excluding case reports, reviews, comments, editorial, and letters and non-English publications, 1,085 records remained. After duplicates were removed, there were 495 records. A total of 483 records were excluded because they were not relevant to the review leaving 12 full-text articles assessed for eligibility. An additional 2 were excluded because of duplicate cohorts. The final review included 10 articles (Fig. 1).

The literature search for prophylactic or risk-reducing salpingo-oophorectomy in *BRCA* carriers identified 1,841 articles through PubMed, OVID MEDLINE, and Scopus. After excluding case reports, reviews, comments, editorial, and letters and non-English publications, 1,285 records remained. After duplicates were removed, there were 582 records. A total of 530 records were excluded because they were not relevant to the review leaving 21 full-text articles assessed for eligibility. An additional 13 were excluded because of duplicate cohorts. The final review included 8 articles (Fig. 2).

Articles were included if (1) they focused on risk reduction after bilateral prophylactic mastectomy or oophorectomy in *BRCA* mutation carriers or cancer occurrence after these procedures; (2) they compared risk-reducing surgery to a surveillance group in *BRCA* mutation carriers; and (3) they examined mortality rates after risk-reducing surgery in *BRCA* mutation carriers. Study quality was assessed using the Grading of Recommendations Assessment, Development and Evaluation Working Group approach (Table 1) using the GRADEpro software.[12,13]

Risk reducing mastectomy in *BRCA* carriers

Breast cancer risk reduction

A total of 10 studies specifically described the incidence of breast cancers after bilateral risk-reducing mastectomies (BRRM).[14–23] They demonstrated a significant risk reduction in the incidence of breast cancer with BRRM ranging from 89.5% to 100% (Table 2). A total of 5 of these studies compared BRRM with surveillance[15,16,18–20] and 5 only