The American Journal of Surgery (2016) 212, 660-669

The American Journal of Surgery®

Association of Women Surgeons

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

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KEYWORDS:
BRCA;
Risk reducing;
Prophylactic;
Mastectomy;
Oophorectomy

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

The authors declare no conflicts of interest.

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Manuscript received February 2, 2016; revised manuscript March 28, 2016

0002-9610/$ - see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjsurg.2016.06.010

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

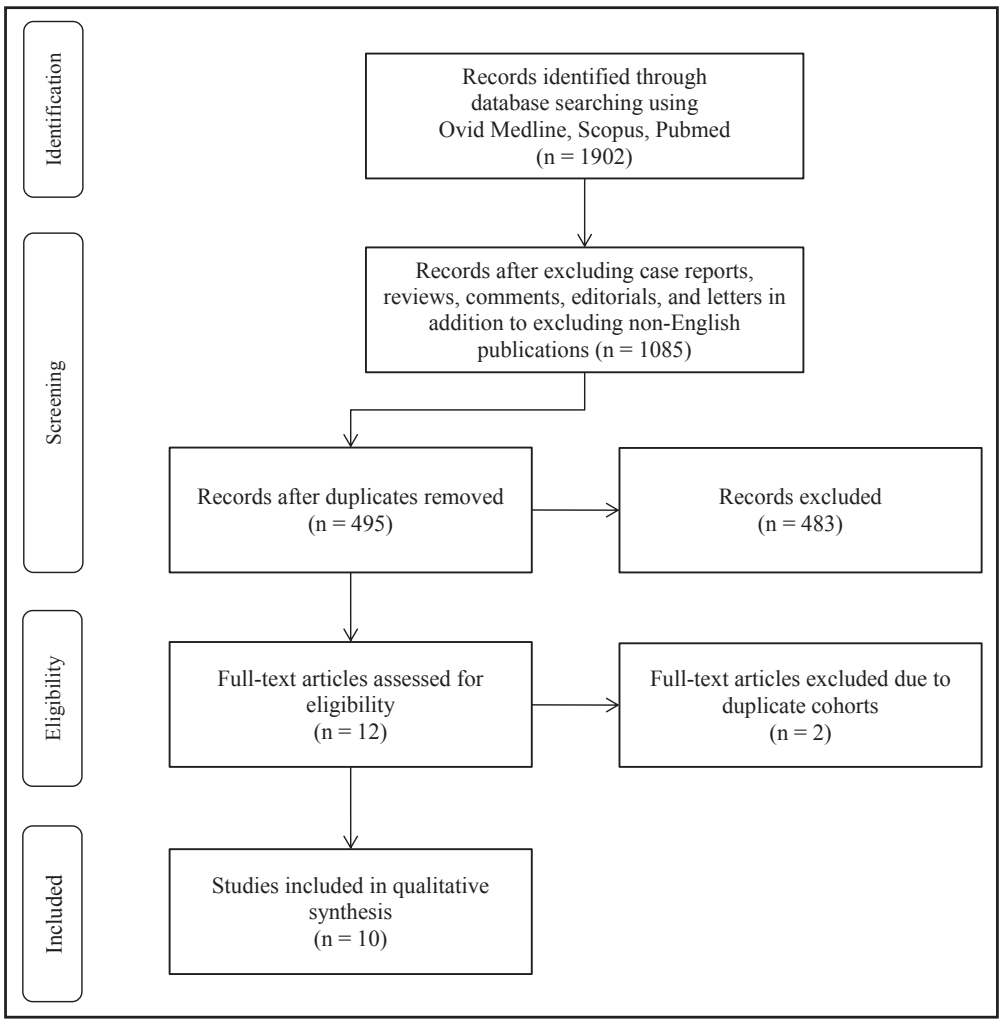

Figure 1 PRISMA flow diagram outlining the literature review process for prophylactic mastectomy in *BRCA* carriers.

described the incidence of occult cancers at surgery and in follow-up after BRRM.[14,17,21–23] Of the 10 studies, 3 did not differentiate between *BRCA1* and *BRCA2* carriers with respect to incidence of breast cancer after BRRM.[14,15,22] However, in a study with one of the largest cohorts of *BRCA* carriers, Domchek et al[16] found that risk-reducing mastectomy was associated with a similar decreased risk of first occurrence of breast cancer in both *BRCA1* and *BRCA2* mutation carriers. No breast cancer events were seen in women who underwent prophylactic mastectomy in a 3-year follow-up period, compared with approximately 6% of women who did not undergo mastectomy. Inclusion of *BRCA* carriers who underwent concurrent RRBSO at the time of BRRM and its effects on breast cancer risk reduction was reported in 4 studies with a varying number of patients who underwent the procedure.[17–20] Rebbeck et al[15] did not specifically report how many patients received an RRBSO but did account for RRBSO in their analysis. They determined bilateral prophylactic mastectomies further reduced the risk of breast cancer in women with intact ovaries by 90% (hazard ratio [HR], .09; 95% confidence interval [CI], .02 to .38), with only 2 women of 105 who had undergone prophylactic mastectomies developing cancer with a mean follow-up of 5.3 years. In women who had concurrent or previous RRBSO, the reduction in breast cancer risk was more profound, with HR .05 (95% CI, .01 to .22). A total of 3 studies did not report the type of mastectomy performed.[14,16,18] Rebbeck et al[15] noted that the patients in their study received either a total (simple) mastectomy, subcutaneous mastectomy, modified radical mastectomy, or radical mastectomy. Ingham et al, Kaas et al, Heemskerk-Gerritsen et al, Peled et al, Manning et al, and Yao et al reported that nearly all patients received a skin-sparing or nipple-sparing mastectomy (NSM) with reconstruction.[17,19–23] Across all studies, only 0 to 3 mutation carriers developed breast cancer after BRRM in both *BRCA1* and *BRCA2* carriers at mean follow-up (range 2 to 13 years; Table 2).

Mortality benefit

Two contemporary studies have examined the effect of BRRM in *BRCA* carriers with respect to mortality. Of all the studies, 1 only examined overall survival. Compared with surgery, Ingham et al found that the HR with BRRM alone was .25 (95% CI, .03 to 1.81, $P = .14$), and the HR was .14 with both BRRM and RRBSO (95% CI, .02 to 1.02, $P = .02$).[19] A second study reported breast cancer–specific

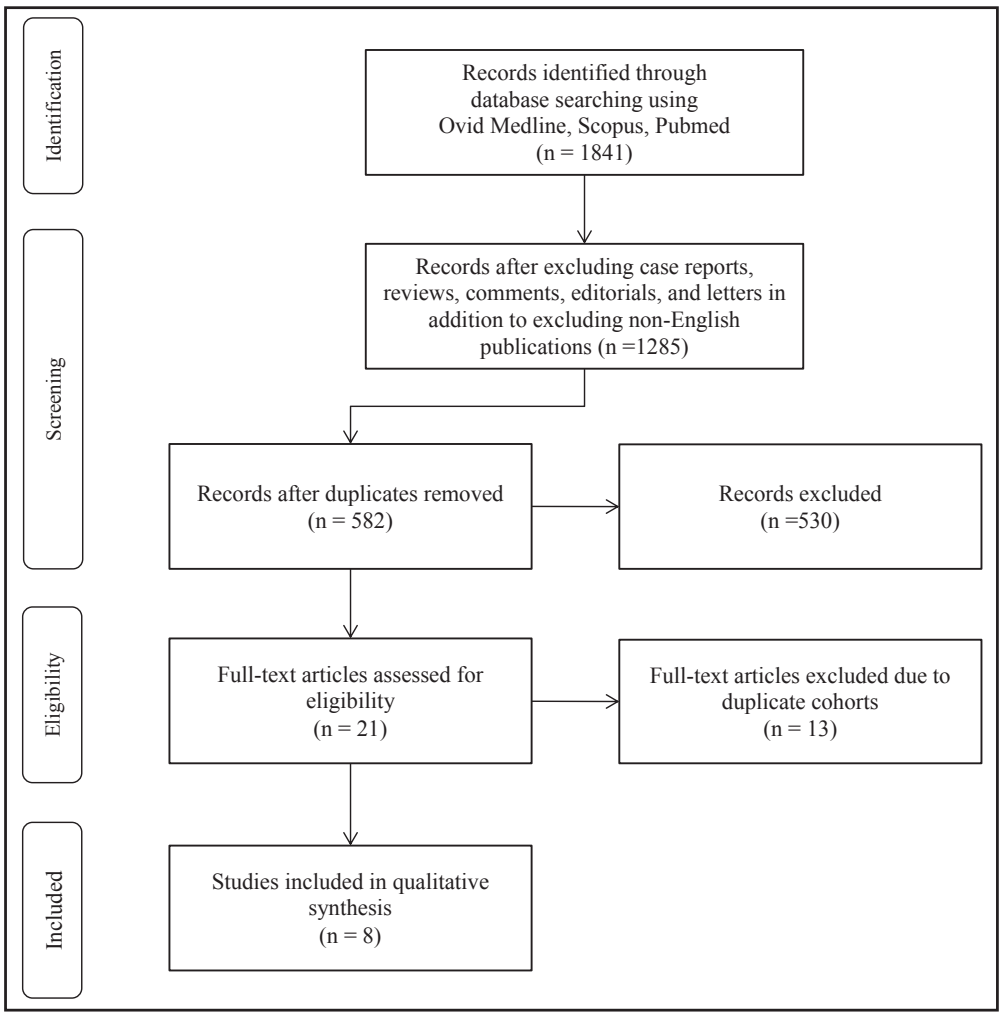

Figure 2 PRISMA flow diagram outlining the literature review process for prophylactic oophorectomy in *BRCA* carriers.

mortality. Heemskerk-Gerritsen et al[20] compared BRRM to a surveillance group and found the BRRM cohort demonstrated no breast cancer–specific survival benefit with an HR of .29 (95% CI, .02 to 2.61). In this cohort of patients, 114 had undergone RRBSO in the mastectomy group and 137 in the surveillance group. The studies had a median follow-up time of 13.3 and 8.5 years, respectively.

Risk reducing salpingo-oophorectomy in *BRCA* carriers

Ovarian cancer risk reduction

A total of 8 studies had cancer occurrence as an outcome, including ovarian cancer, fallopian tube cancer, and primary peritoneal carcinoma.[16,24–30] Of all the studies, 6 compared surveillance to surgery,[16,24,26,28–30] (Table 3) whereas 2 reported the prevalence of occult cancers and risk of primary peritoneal carcinoma after RRBSO.[25,27]

The 6 studies comparing RRBSO to surveillance reported a profound reduction in ovarian cancer risk, ranging from 72% to 88%.[16,23,24,26–28] In the total of 4,504 *BRCA* carriers across all 6 studies who underwent surveillance, 233 (5.2%) developed ovarian cancer at the time of follow-up (range 2.1 to 6.8 years). In the 5,484 women who underwent surgery, follow-up ranged from 2.0 to 8.2 years. During that time, 47 women developed primary peritoneal carcinoma (.97%).[16,24,26,28–30] Kauff et al[26] were the only investigators to stratify reduction in ovarian cancer risk by the type of mutation. In their cohort of 792 women, RRBSO was associated with an 85% reduction in ovarian cancer risk in *BRCA1* carriers (HR, .15; 95% CI, .03 to .41). Although no cancers were seen at the time of follow-up in *BRCA2* carriers, they were unable to calculate HRs because of lack of events.

Mortality benefit

A total of 2 studies examined the effect of RRBSO on mortality in *BRCA* carriers. In the largest prospective multicenter analysis of 5,783 *BRCA* carriers, Finch et al[24] reported a 69% reduction in all-cause mortality using RRBSO; this was adjusted for age, parity, use of oral contraceptives, and history of breast cancer. The type of mutation did not appear to affect the results as benefit was seen

Table 1 GRADE analysis to assess quality of data for risk reducing mastectomy and oophorectomy in *BRCA* carriers

GRADE analysis							
Quality assessment							
Outcome	No. of participants (studies) follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect	Overall quality of evidence
Breast cancer incidence with prophylactic mastectomy vs surveillance	3,007 (10 observational studies)	Not serious	Not serious	Not serious	Not serious	Large	⊕⊕⊕◯ Moderate
Mortality with prophylactic mastectomy vs surveillance	1,153 (2 observational studies)	Not serious	Not serious	Serious (1 study used all-cause mortality as an end point, whereas the other used breast cancer–specific mortality)	Not serious	NA	⊕◯◯◯ Very low
Ovarian cancer incidence with bilateral salpingo-oophorectomy vs surveillance	9,988 (6 observational studies)	Not serious	Not serious	Not serious	Not serious	Large	⊕⊕⊕◯ Moderate
Mortality with bilateral salpingo-oophorectomy vs surveillance	8,265 (2 observational studies)	Not serious	Not serious	Not serious	Not serious	NA	⊕⊕◯◯ Low

GRADE working group grades of evidence—High quality: We are very confident that the true effect lies close to that of the estimate of the effect; moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

NA = not applicable.

Table 2 Breast cancer risk reduction and new breast cancers after risk-reducing mastectomy

Study	Number of patients	Occult breast cancers	RRBSO	Breast cancer after BRRM	Length of follow-up	Risk reduction
Hartmann et al[14]	18 Mastectomy	0 (0%) 0 in BRCA1 and BRCA2	No	0	13.4 y (median)	89.5%–100%
Rebbeck et al[15]	105 Mastectomy 378 Surveillance	0 (0%) 0 in BRCA1 and BRCA2	Not stated	2 in the mastectomy group 184 in the surveillance group	5.3 y (mean, BRRM group) 7.5 y (mean, control group)	Reduction in breast cancer risk HR, .09 (95% CI, .02–.38) with intact ovaries HR, .05 (95% CI, .01–.22) with concurrent or prior RRBSO
Domchek et al[16]	75 Mastectomy 585 Surveillance	3 (4.0%) 2 in BRCA1 1 in BRCA2	No	0 in mastectomy group 34 in surveillance group	3 y	—
Kaas et al[17]	147 Mastectomy	7 (4.8%) 4 in BRCA1* 3 in BRCA2†	80	0	6.1 y for BRCA1 (mean) 3.7 y for BRCA2 (mean)	—
Skytte et al[18]	96 Mastectomy 211 Surveillance	1 (1.0%)	67 in mastectomy group 88 in surveillance group	3 in mastectomy group (all BRCA1 positive) 16 in surveillance group	378.7 y of at-risk time in the mastectomy cohort 934.6 y of at-risk time in the no-mastectomy cohort	Effect on breast cancer rate comparing BRRM to no BRRM HR, .394 (95% CI, .115–1.355, P =.14)
Ingham et al[19]	126 Mastectomy 457 Surveillance	5 (4.0%) 2 in BRCA1 3 in BRCA2	68 in mastectomy group	1 in mastectomy group (BRCA2 positive) 202 in surveillance group	13.3 y (median)	Mortality compared with no surgery With BRRM alone HR, .25 (95% CI, .03–1.81 P =.14) With BRRM and RRBSO HR, .14 (95% CI, .02–1.02 P =.02)
Heemskerk-Gerritsen et al[20]	212 Mastectomy 358 Surveillance	6 (2.8%) 4 in BRCA1 2 in BRCA2*	114 mastectomy group 137 surveillance group	1 in mastectomy group (BRCA1 positive) 57 in surveillance group	8.5 y (median)	Breast cancer–specific mortality HR, .29 (95% CI, .02–2.61)
Peled et al[23]	26 Mastectomy	1 (3.8%)	Not stated	0	51 mo (mean)	
Manning et al[21]	63 Mastectomy	8 (12.7%)*	Not stated	0	26 mo (median)	
Yao et al[22]	150 Mastectomy	4 (2.7%)	Not stated	1	32.6 mo (mean)	

*Ductal carcinoma in situ (DCIS) only.
†Two cases of DCIS, 1 invasive carcinoma.

Table 3 Incidence of cancers in women undergoing surveillance and RRBSO and comparison of risk reduction

Study	Number of patients	Incidence of occult ovarian cancers at RRBSO	Incidence of ovarian cancers in surveillance group	Incidence of primary peritoneal cancer after RRBSO	Length of follow-up	Risk reduction analysis
Finch et al[24]	2,270 Surveillance 3,513 RRBSO	46 (1.5%) 44 BRCA1 2 BRCA2	108 (4.8%) 98 BRCA1 10 BRCA2	32 (1.9%)	5.6 y (mean)	Ovarian cancer risk HR, .20 (95% CI, .13–.30) Mortality (all cause) HR, .31 (95% CI, .26–.38) Both adjusted for age, parity, OCP use, BRCA, hx breast ca BRCA1 HR, .30 BRCA2 HR, .33
Domchek et al[16]	1,678 Surveillance 939 RRBSO	22 (2.3%) 17 BRCA1 5 BRCA2	98 (5.8%) 76 BRCA1 22 BRCA2	10 (1%) 10 BRCA1 0 BRCA2	4.3 y Surveillance (mean) 3.7 y RRBSO (mean)	Ovarian cancer risk HR, .28 no prior hx breast ca (95% CI, .12–.69) HR, .14 with prior hx breast ca (95% CI, .04–.59) Mortality (all cause) HR, .40 (95% CI, .26–.61) BRCA1 HR, .38 BRCA2 HR, .52 (not significant) Mortality (ovarian cancer specific) HR, .21 (95% CI, .06–.80) BRCA1 HR, .22 BRCA2 no events
Kauff et al[26]	283 Surveillance 509 RRBSO	15 (2.9%)	12 (4.2%) 10 BRCA1 2 BRCA2	3 (.6%) 3 BRCA1 0 BRCA2	3.1 y Surveillance (mean) 3.3 y RRBSO (mean)	Ovarian cancer risk HR, .12 (95% CI, .03–.41) BRCA1 HR, .15 BRCA2 no events
Evans et al[28]	160 Surveillance 160 RRBSO	3 (1.9%) 2 BRCA1 1 BRCA2	10 (6.3%) 9 BRCA1 1 BRCA2	0 (0%)	6.8 y Surveillance (mean) 8.2 y RRBSO (mean)	Unable to calculate secondary to no events after RRBSO
Schmeler et al[29]	41 Surveillance 65 RRBSO	2 (3%)	0 (0%)	0 (0%)	2.1 y Surveillance (mean) 2.6 y RRBSO (mean)	Unable to calculate secondary to no events in either group
Kauff et al[30]	72 Surveillance 98 BSO	3 (3.1%)	5 (6.9%)	1 (1%)	2.2 y Surveillance (mean) 2.0 y RRBSO (mean)	Ovarian cancer risk HR, .15 (95% CI, .02–1.31) Not distinguished by BRCA

Ca = cancer; Hx = history; OCP = oral contraceptive pill.

in both *BRCA1* and *BRCA2* carriers (HR, .30 and HR, .33, respectively). Similar findings were seen in a prospective multicenter cohort of 2,617 *BRCA* carriers as reported by Domchek et al.[16] This study, affiliated with the Prevention and Observation of Surgical Endpoints consortium, demonstrated a reduction in both ovarian cancer–specific and all-cause mortality in patients who underwent surgery (HR, .40 and HR, .21, respectively). This effect was significant for *BRCA1* carriers but unable to be calculated in *BRCA2* carriers because of low number of events.[16]

Comments

This systematic review addresses the question of whether RRBSO and/or BRRM is beneficial for *BRCA* mutation carriers with respect to risk reduction and mortality. Primary studies of *BRCA* mutation carriers who have undergone BRRM in this review demonstrate a significant risk reduction in breast cancer incidence. The risk of breast cancer after BRRM is less than 3%, and the risk reduction appears to be equal in both *BRCA1* and *BRCA2* mutation carriers (Table 2).[14–23] Because the event rate is low, it is difficult to compare rates of breast cancer after BRRM in *BRCA1* vs *BRCA2* mutation carriers. This risk reduction was seen in studies whether the carriers had undergone an RRBSO[17–20] or did not.[14,16] It is likely that the presence of RRBSO contributes to an even greater risk reduction in breast cancer incidence after BRRM.[15] The data we evaluated also demonstrate that compared with surveillance, RRBSO is highly effective in reducing incidence of ovarian cancer in women with *BRCA* mutations. The risk of peritoneal carcinoma after RRBSO is less than 1.9%.[16,24–30] The data also suggest that this reduction in cancer incidence translates to a substantial improvement in all-cause and ovarian cancer–specific mortality.[16,24] The reduction in both cancer incidence and mortality appears to be more significant in *BRCA1* carriers. Although there appears to be a benefit in *BRCA2* carriers, there are too few events to reach statistical significance.[16,24,26]

No randomized data exist, so our analysis is limited to observational studies that possess inherent bias. Meta-analysis of the data could not be performed because of the heterogeneity of the studies. There is significant variation between cohort sample sizes and very short follow-up. Additionally, data regarding specifics of surveillance protocols are limited, including frequency and compliance of screening and surgical approach (nipple sparing or skin sparing, use of sentinel node biopsy, laparoscopic vs open, ± hysterectomy, removal of intramural fallopian tubes, and use of peritoneal washings). One would assume that patients were clinically asymptomatic at the time of surgery, but this cannot be evaluated based on the data set and could potentially skew the results. Inconsistent stratification of results by *BRCA* mutation type has resulted in difficulty assessing whether the magnitude of the benefit is similar for both mutations. Furthermore, some study groups include women with a history of cancer, which could potentially affect outcomes of all-cause mortality. Taking these limitations into account, future studies should standardize their reporting such that a meta-analysis can be completed to determine an HR for risk reduction and mortality.

Bilateral risk-reducing mastectomy

Although the BRRM studies reviewed demonstrated a significant risk reduction, they also found a low incidence of occult ($\leq$5%) carcinoma at the time of BRRM.[14–23] The presence of occult tumors highlights the importance of pathologic analysis of all prophylactic mastectomy specimens. However, because the risk of an occult tumor is so low, with some of these being carcinoma in situ, a sentinel node biopsy at the time of prophylactic mastectomy in *BRCA* mutation carriers should be optional and not required as has been demonstrated with prophylactic mastectomies in non-*BRCA* mutation carriers as well.[31]

There were 2 studies with more than 1 breast cancer after BRRM. Rebbeck et al[15] reported 2 breast cancers in patients who had undergone BRRM with subcutaneous mastectomies. Subcutaneous mastectomies leave a substantial amount of tissue compared with a total mastectomy leaving the individual with a higher potential to develop cancer. Thus, the procedure does not provide maximal risk reduction. Skytte et al reported 3 breast cancers after BRRM but did not report the type of mastectomy that was performed. However, in contemporary series of skin-sparing and nipple-sparing mastectomies, the incidence of breast cancer after BRRM is low.[17,19–23] With the advent of the cosmetically appealing NSM, some surgeons have been particularly reticent to adopt this procedure in *BRCA* mutation carriers because of concerns about the density of ducts in the nipple and the future risk of carcinoma. Yao et al[22] found 4 incidental cancers in the largest series of 150 mutation carriers who underwent nipple-sparing BRRM. At follow-up, only 1 cancer event occurred in the prophylactic group which was remote from the nipple areolar complex. Their findings suggest that NSM is oncologically safe and are supported by other smaller series.[21,23,32]

The reduction in breast cancer risk with BRRM, however, has not translated into a survival benefit in primary studies, likely because of short-term follow-up.[19,20] BRRM may eventually demonstrate a significant survival advantage given the reduction in breast cancer incidence as longer follow-up of these mutation carriers becomes available. However, in a decision analysis, Schrag et al[33] compared prophylactic mastectomy and prophylactic oophorectomy with no prophylactic surgery among women who carry mutations in the *BRCA1* or *BRCA2* gene. Using a Markov model, the authors constructed hypothetical cohorts of women using early estimates of the cumulative risk of cancer among *BRCA1 and BRCA2* mutation carriers to calculate the effect of prophylactic surgery on survival. Their analysis demonstrated a much greater increase in life expectancy with prophylactic mastectomy than prophylactic oophorectomy. The authors

do note that one of the limitations of their analysis is that calculated gains in life expectancy have to be interpreted carefully and that an increase of 4 years in life expectancy, for example, does not mean that a specific individual will have an absolute gain of 4 years to her life.

Although providing a significant risk reduction, prophylactic surgery is not appropriate for every woman. Current guidelines recommend yearly mammogram and MRI alternating every 6 months along with clinical examination for women who do not wish to pursue BRRM.[9] Unlike surgery, surveillance with breast imaging does not reduce the risk of breast cancer but may help ensure early detection. This decision must be individualized with a discussion between the surgeon and the patient.

Risk reducing bilateral salpingo-oophorectomy

Although most patients are asymptomatic at the time of preventive surgery, occult cancers may be detected in this high-risk population (1.9% to 9.1%).[16,24–30,34] The ovary is the most common site, but the fallopian tube may be the source of pathology in up to 90%. Total removal of both ovaries and fallopian tubes with careful sectioning and microscopic examination is indicated to identify occult disease.[25] Pelvic washings and laparoscopic examination of the peritoneal surfaces are also encouraged to identify further sites of occult metastasis.[35] Patients with *BRCA1* mutations are more likely to be diagnosed with occult disease compared with *BRCA2* carriers (4.2% vs .6%, respectively). Women with *BRCA1* mutations are more likely to develop malignant pathology at a younger age, so one would expect an increase in occult cancers at time of RRBSO compared with *BRCA2* carriers.[24]

Current national guidelines recommend consideration of RRBSO after completion of childbearing, "typically between 35 and 40 years."[9] However, determining the most appropriate time of prophylactic surgery in women with future reproductive desires may be challenging. There is benefit to identifying occult disease before the advent of symptoms as the 5-year survival for women with occult carcinomas is superior to women with cancer that was detected clinically (91.6% vs 54.4%, $P<.01$). The risk of developing ovarian cancer does increase with age. As observed by Finch et al,[24] if a woman with *BRCA1* mutation waits until age 40 to undergo preventive surgery, she has a 4% risk of being diagnosed with ovarian cancer (either occult disease diagnosed at the time of surgery or clinically before). If she delays surgery until age 50, her risk increases to 14%.

For women with intact ovaries, surveillance historically included transvaginal ultrasound and CA-125 levels twice yearly. Current data have shown that the ability of these tests to detect early-stage ovarian cancers in premenopausal women is poor, and false-positive rates are high.[36] Although they may be performed at the clinician's discretion, they are no longer endorsed as a reasonable alternative to surgery.[9]

Individualized decision making

With the increasing indications for genetic testing that are constantly changing,[9] more women will be diagnosed with *BRCA* mutations. Currently, it is not feasible to personalize *BRCA* carriers' cancer risk based on the specific deleterious mutation. Instead, average risk among a group of carriers with a representative mix of mutations in the population must be calculated. One of the most comprehensive studies of *BRCA1* and *BRCA2* penetrance found that the mean cumulative cancer risks for mutation carriers at 70 years of age were as follows: a breast cancer risk of 57% for *BRCA1* mutation carriers and 49% for *BRCA2* mutation carriers and an ovarian cancer risk of 40% for *BRCA1* mutation carriers and 18% for *BRCA2* mutation carriers.[37] Using this information, an at-risk individual can be counseled about her breast and ovarian cancer risk based on current age and possible surgical risk reduction strategies. Clinical management of these patients at increased risk for breast and ovarian cancer is multifaceted and complex, requiring consideration of risk and quality of life. Both surgeries are irreversible and have potential for short-term morbidity, such as surgical complications, symptoms of estrogen deprivation, and body image issues. Most studies do not address the impact of these surgeries on quality of life or noncancer-related morbidity. The literature is also limited on factors that influence a *BRCA* mutation carrier's decision to undergo prophylactic surgery. Studies have reported that a family history of breast or ovarian cancer, parity, and age have been associated with choosing to undergo risk reducing surgery.[30,38–42] Although, this topic was not the focus of this review, it highlights the limitations of the current data for guiding surgeons in discussions with their patients in the era of patient-centered care.

Conclusions

In summary, our systematic review aimed to determine whether prophylactic surgery improves outcomes in unaffected *BRCA* carriers. The data presented here confirm both BRRM and RRBSO result in a reduction in both breast and ovarian cancers. Improvement in ovarian cancer–related and all-cause mortality was seen with RRBSO with moderate-quality data. However, this improvement was not seen with BRRM as the data were of low quality. Need for longer follow-up and heterogeneity in reporting contribute to the poor quality of the data for survival benefit with BRRM. Future studies should focus on consistent reporting of outcomes with longer follow-up to perform an adequate meta-analysis of risk and mortality. Other areas of research should focus on patient quality of life after prophylactic surgery and factors that influence *BRCA* carrier decision making with prophylactic surgery. Ultimately, the choice to undergo surgery is patient specific and related to factors such as self-image, desire for future children, and individualized risk for breast and ovarian cancers.

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