Effectiveness of Prophylactic Surgeries in \textit{BRCA1} or \textit{BRCA2} Mutation Carriers: A Meta-analysis and Systematic Review

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**Abstract**

**Purpose:** To systematically investigate the effectiveness of prophylactic surgeries (PS) implemented in women carrying \textit{BRCA1/2} mutations.

**Experimental Design:** The PubMed database was searched till August 2014 and 15 studies met the inclusion criteria. Fixed- or random-effects models were conducted according to study heterogeneity. We calculated the pooled relative risks (RR) for cancer risk or mortality along with 95% confidence intervals (CI).

**Results:** Prophylactic bilateral salpingo-oophorectomy (PBSO) and bilateral prophylactic mastectomy (BPM) were both associated with a decreased breast cancer risk in \textit{BRCA1} mutation carriers (RR, 0.552; 95% CI, 0.448–0.682; RR, 0.114; 95% CI, 0.041–0.317, respectively). Similar findings were observed in \textit{BRCA1} and \textit{BRCA2} mutation carriers separately. Moreover, contralateral prophylactic mastectomy (CPM) significantly decreased contralateral breast cancer incidence in \textit{BRCA1/2} mutation carriers (RR, 0.072; 95% CI, 0.035–0.148). Of note, PBSO was associated with significantly lower all-cause mortality in \textit{BRCA1/2} mutation carriers without breast cancer (HR, 0.349; 95% CI, 0.190–0.639) and those with breast cancer (HR, 0.432; 95% CI, 0.318–0.588). In addition, all-cause mortality was significantly lower for patients with BPM than those without (HR, 0.512; 95% CI, 0.368–0.714). However, BPM was not significantly associated with reduced all-cause mortality. Data were insufficient to obtain separate estimates of survival benefit with PS in \textit{BRCA1} or \textit{BRCA2} mutation carriers.

**Conclusions:** \textit{BRCA1/2} mutation carriers who have been treated with PS have a substantially reduced breast cancer incidence and mortality. *Clin Cancer Res;* 22(15); 3971–81. ©2016 AACR.

**Introduction**

Women, who carry a deleterious mutation in breast cancer susceptibility gene 1 (\textit{BRCA1}) or breast cancer susceptibility gene 2 (\textit{BRCA2}), have a high lifetime risk of developing breast cancer, clearly above the risk for the general population. By the age of 70 years, the breast cancer risk is 40% to 80% for \textit{BRCA1} or \textit{BRCA2} mutation carriers (1, 2). Besides, women with \textit{BRCA1} or \textit{BRCA2} mutation and a history of primary breast cancer (PBC) have a significantly elevated risk of developing contralateral breast cancer (CBC). The estimated cumulative lifetime risk of CBC is 20% to 83% for \textit{BRCA1/2} mutation carriers (3–7). \textit{BRCA1/2} mutation carriers are advised to consider different risk-reducing strategies, including surveillance (breast self-examination, clinical breast examination, screening using mammography and breast magnetic resonance imaging), chemoprevention and prophylactic surgery (8). However, the risk-reducing methods vary in their effectiveness. For about 20 years, researchers have studied whether prophylactic surgery can reduce the cancer and mortality risk in \textit{BRCA1/2} mutation carriers.

Prophylactic mastectomy (PM) implies either a bilateral prophylactic mastectomy (BPM) in high-risk unaffected women or a contralateral prophylactic mastectomy (CPM) after a unilateral therapeutic mastectomy. It has been demonstrated that BPM is a highly effective strategy to reduce the risk of breast cancer at high risk (9, 10). CPM is also considered to be the most effective option for CBC risk reduction (11, 12). However, the ultimate goal of PM is to improve survival, eventually being the reason for a woman to decide for this drastic intervention. A prospective cohort study carried out by Heemskerk-Gerritsen and colleagues (13) showed that after BPM, all-cause mortality and breast cancer–specific mortality rates were reduced, compared with surveillance, but significant survival benefits could not be claimed. On the other hand, data on survival of PBC patients with \textit{BRCA1/2} mutation who opt for subsequent CPM were inconsistent. Some studies showed improved survival after CPM (14, 15), while others did not (11, 16).

Prophylactic bilateral salpingo-oophorectomy (PBSO) has also been shown to reduce breast cancer risk in mutation...
Translational Relevance
This report compiles data from 15 studies independently. In this article, we identified that prophylactic bilateral salpingo-oophorectomy (PBSO) and bilateral prophylactic mastectomy (BPM) were both associated with a decreased breast cancer risk in breast cancer susceptibility gene 1 (BRCA1) or breast cancer susceptibility gene 2 (BRCA2) mutation carriers. Similar findings were observed in BRCA1 and BRCA2 mutation carriers separately. Moreover, contralateral prophylactic mastectomy (CPM) significantly decreased contralateral breast cancer incidence in BRCA1/2 mutation carriers. Notably, PBSO was associated with significantly lower all-cause mortality in BRCA1/2 mutation carriers without breast cancer and those with breast cancer. In addition, all-cause mortality was significantly lower for patients with CPM than those without. However, BPM was not significantly associated with reduced all-cause mortality. The results could be utilized by health care professionals.

Materials and Methods
Search strategy
To identify all reports of risk-reducing surgery, including PBSO, BPM, and CPM in BRCA1 or BRCA2 mutation carriers, we searched the PubMed database using the search terms “breast cancer” and “BRCA1” or “BRCA2.” The search yielded 4,574 studies that were published between August 2014 and September 1999.

Three reviewers independently evaluated titles and abstracts of the identified papers. We also reviewed the references in identified articles for possible inclusions. Only those published studies in English language with full-text articles were included in this meta-analysis. The research did not reveal any additional unpublished studies.

Criteria for inclusion and exclusion
Studies were included in our meta-analysis and systematic review if they met the following criteria: (i) case–control studies or cohort studies, (ii) both case and control subjects were women who carried a deleterious BRCA1 or BRCA2 mutation, (iii) studies provided estimates of breast cancer risk reduction or mortality due to prophylactic surgeries, including PBSO, BPM, and CPM, and (iv) relative risk (RR) and the corresponding 95% confidence interval (CI) were reported, or sufficient published data for estimating a RR with 95% CI. Articles reporting only on the utilization of the prophylactic strategies by BRCA1 or BRCA2 mutation carriers were excluded. Studies of attitudes, reactions, screening, and chemoprevention practices in BRCA1/2 mutation carriers were also excluded.

When two or more articles had overlapping study samples, the most recent article based on the largest study population was selected. Of the studies identified here, sample overlaps were noted in the studies of Rebbeck and colleagues (24, 25), Kauff and colleagues (20, 26), Domchek and colleagues (23, 27), and Finkelman and colleagues (21). Finkelman and colleagues (21) was more recent with larger sample size than the other studies, it was chosen for inclusion in the meta-analysis. However, among articles with overlapping study samples, the ones with different subgroup analysis (20) or different research destinations (23) were also included. Although we made every attempt to eliminate redundancy in the data represented in the meta-analysis, we cannot rule out the possibility that a few individuals had participated in more than one study.

Data extraction
Data were carefully extracted from all the eligible studies independently by the investigators. Disagreement was solved by a discussion. The following data were extracted from the included studies if available: first author’s name, year of publication, type of study (retrospective or prospective, cohort or case–control), patient source, sample size (number of total subjects with or without prophylactic surgery, number of new PBCs, and number of BCs), mean age (at prophylactic surgery and at breast cancer), and mean time of follow-up. We then extracted study-specific estimates of RRs (ORs HRs) and the 95% CIs of breast cancer risk, CBC risk or mortality for women with PBSO, BPM, or CPM versus no prophylactic surgery.

Quality assessment
The quality of the studies was assessed using the validated Newcastle-Ottawa Scale (NOS) for nonrandomized studies,
including case–control and cohort studies. Though NOS has been widely utilized, it has not been published in peer-reviewed journals so far. Separate NOS scales were developed for cohort and case–control studies. NOS awards eight points to each cohort study (four for quality of selection, one for comparability, and three for quality of outcome). A study can be awarded a maximum of one star for each point within the selection and outcome categories, and a maximum of two stars can be given for comparability. Besides, NOS also awards eight points to each case–control study (four for quality of selection, one for comparability, and three for quality of exposure). A study can be awarded a maximum of one star for each point within the selection and exposure categories, and a maximum of two stars can be given for comparability. We considered studies with scores of more than 7 as high-quality studies, and those with scores of 7 or less as low-quality studies.

Statistical analysis
We carried out separate meta-analysis in BRCA1 mutation carriers, BRCA2 mutation carriers, and among women who carried either BRCA1 or BRCA2 mutation (denoted BRCA1/2).

We calculated the pooled rate for each outcome (cancer risk or mortality) along with 95% CI. We proceeded to the calculation of pooled effect estimates if there were at least two studies with sufficient data in each outcome of interest. Crude RR with 95% CI was used to assess the association between BPM and breast cancer risk, and the association between CPM and CBC risk. HR (as published in the original reports) with 95% CI was used as a common measure of the association between BPSO and breast cancer risk and mortality, and the association between BPM and mortality.

Statistical heterogeneity among studies included in the meta-analysis was assessed using Q statistic (28). Heterogeneity was considered as $P < 0.05$. Two techniques were used to estimate the summary RR estimates. When heterogeneity among studies was absent, the fixed-effects model (the Mantel–Haenszed method; ref. 29) was used to calculate the pooled RRs. Otherwise, a random-effects model (the DerSimonian and Laird method; ref. 30) was selected. Finally, the possibility of publication bias was investigated through Funnel plots, the Begg–Mazumdar adjusted rank correlation test (31) and the Egger regression asymmetry tests (32). $P < 0.05$ was considered statistically significant.

All the $P$ values were two sided. All analyses were conducted using the software Stata version 11.0 (Stata Corporation).

Results
Description of the included studies
Our initial search yielded 4,574 articles, of which we screened the titles and abstracts. Studies (139) were selected for further review. Finally, 15 unique studies were initially selected as
potentially appropriate for meta-analysis inclusion. Our search strategy is presented in Fig. 1.

The details of eligible studies are summarized in Tables 1 and 2. As can be seen in this summary, the studies that formed the basis for this meta-analysis included prospective cohort studies, retrospective cohort studies, and case–control studies. Limitations of the currently available data regarding prophylactic surgery in BRCA1 or BRCA2 mutation carriers include variable study designs, small sample size for some studies, and different durations of post-surgery follow-up times. We have summarized the results of the meta-analysis when two or more eligible studies could be meta-analyzed, as well as the individual articles where only a single study could be analyzed, as well as the individual articles where only a single study could be meta-analyzed.

Thirteen studies had a quality score higher than 7 points, and 2 studies had a quality score equal to 7 points (Table 1).

**Prophylactic surgery and breast cancer risk**

**PBSO and breast cancer risk.** Three nonoverlapping studies (17, 19, 21) estimated the risk of breast cancer in BRCA1/2 mutation carriers who were treated with PBSO relative to BRCA1/2 mutation carriers who did not receive any prophylactic surgery. In total, 7,323 women with BRCA1/2 mutation were included in the meta-analysis. PBSO was associated with a decreased risk of breast cancer in BRCA1/2 mutation carriers (summary RR, 0.552; 95% CI, 0.448–0.682; Table S1, Figure 2A). Four nonoverlapping studies (17–19, 21) estimated the risk reduction associated with PBSO for breast cancer in BRCA1 mutation carriers, giving a summary RR estimate of 0.47 (95% CI, 0.348–0.636; Table S1, Figure 2B). And 3 non-overlapping studies (17, 19, 20) estimated the risk reduction associated with PBSO in breast cancer in BRCA1 mutation carriers, giving a summary RR estimate of 0.468 (95% CI, 0.263–0.835; Table S1, Figure 2C).

**BPM and breast cancer risk.** Six nonoverlapping studies (10, 13, 22, 23, 33, 34), which included 2,555 participants, estimated the risk of breast cancer in BRCA1/2 mutation carriers treated with BPM relative to BRCA1/2 mutation carriers who did not receive any prophylactic surgery. Compared with controls, the occurrence of breast cancer was significantly reduced in BRCA1/2 mutation carriers who received BPM (summary RR estimate of 0.636; Table S1, Figure 2C).

### Table 1. Characteristics of 15 studies included in this meta-analysis

<table>
<thead>
<tr>
<th>Study (ref)</th>
<th>First author</th>
<th>Year</th>
<th>Study design</th>
<th>NOS points</th>
<th>Main study objective</th>
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</thead>
<tbody>
<tr>
<td>33</td>
<td>Meijers-Heijboer</td>
<td>2001</td>
<td>PC</td>
<td>8</td>
<td>Influence of BPM in B1/2 patients on BC risk</td>
</tr>
<tr>
<td>10</td>
<td>Rebbeck</td>
<td>2004</td>
<td>PC</td>
<td>9</td>
<td>Influence of BPM in B1/2 patients on BC risk</td>
</tr>
<tr>
<td>17</td>
<td>Eisen</td>
<td>2005</td>
<td>CC</td>
<td>9</td>
<td>Influence of PS in B1, B2, or B1/2 patients on BC risk</td>
</tr>
<tr>
<td>18</td>
<td>Kramer</td>
<td>2005</td>
<td>PC</td>
<td>7</td>
<td>Influence of BPM in B1 patients on BC risk</td>
</tr>
<tr>
<td>11</td>
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<td>2005</td>
<td>PC</td>
<td>9</td>
<td>Influence of BPM in B1/2 patients on CBC risk</td>
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<tr>
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<td>RC</td>
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<td>Influence of PS in B1/2 patients on BC risk</td>
</tr>
<tr>
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<td>2008</td>
<td>PC</td>
<td>8</td>
<td>Influence of PS in B1 or B2 patients on BC risk</td>
</tr>
<tr>
<td>23</td>
<td>Dornchek</td>
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<td>Influence of PS in B1 or B2 patients on BC risk and mortality</td>
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<tr>
<td>34</td>
<td>Skytte</td>
<td>2011</td>
<td>PC</td>
<td>8</td>
<td>Influence of BPM in B1 or B2 patients on BC risk</td>
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<td>21</td>
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<td>PC</td>
<td>9</td>
<td>Influence of PS in B1/2 patients on BC risk</td>
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<tr>
<td>22</td>
<td>Heemskerk-Gerritsen</td>
<td>2013</td>
<td>PC</td>
<td>9</td>
<td>Influence of PS in B1 or B2 patients on BC risk and mortality</td>
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<tr>
<td>16</td>
<td>Evans</td>
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<td>PC</td>
<td>9</td>
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<tr>
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<td>14</td>
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**Table 2. Characteristics of patients of individual studies included in this meta-analysis**

<table>
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<tr>
<th>Study (ref)</th>
<th>First author</th>
<th>Year</th>
<th>Patients source</th>
<th>No. with/without PS</th>
<th>Mean follow-up (y) PS/no PS</th>
<th>Mean age at BC (y) PS/no PS</th>
<th>Mean age at PS (y)</th>
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<tr>
<td>33</td>
<td>Meijers-Heijboer</td>
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<td>SIS</td>
<td>76/63</td>
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<td>NR</td>
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<tr>
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<td>2004</td>
<td>NAEMC</td>
<td>59/305</td>
<td>NR</td>
<td>NR</td>
<td>B1/2: 5.5/6.7</td>
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<tr>
<td>17</td>
<td>Eisen</td>
<td>2005</td>
<td>IMC</td>
<td>106/339</td>
<td>NR</td>
<td>129/2341</td>
<td>B2: 20.6</td>
</tr>
<tr>
<td>18</td>
<td>Kramer</td>
<td>2005</td>
<td>NAMC</td>
<td>33/65</td>
<td>NR</td>
<td>Mean 16.5</td>
<td>41.9</td>
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<tr>
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<td>TIS</td>
<td>79/69</td>
<td>60/55</td>
<td>19/14</td>
<td>7.4/10.5</td>
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<tr>
<td>19</td>
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<td>EMC</td>
<td>55/1601</td>
<td>NR</td>
<td>325/173</td>
<td>184/140</td>
</tr>
<tr>
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<td>2008</td>
<td>IMC</td>
<td>509/283</td>
<td>325/173</td>
<td>184/140</td>
<td>3.2</td>
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<td>23</td>
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<td>2010</td>
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<td>32/213</td>
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<td>2011</td>
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<td>96/211</td>
<td>67/334</td>
<td>29/77</td>
<td>Max &gt; 7</td>
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<tr>
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<td>NR</td>
<td>NR</td>
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<td>58/457</td>
<td>29/219</td>
<td>29/238</td>
<td>Median 13.3</td>
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<tr>
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<td>2013</td>
<td>SIS</td>
<td>43/473</td>
<td>NR</td>
<td>NR</td>
<td>Median 9.7/8.6</td>
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<tr>
<td>15</td>
<td>Metcalfe</td>
<td>2014</td>
<td>IMC</td>
<td>181/209</td>
<td>NR</td>
<td>13</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Abbreviations:** B1, BRCA1; B2, BRCA2; B1/2, BRCA1 or BRCA2; BC, breast cancer; CC, case–control study; PC, prospective cohort study; RC, retrospective cohort study; SIS, single institution study; TIS, two institutions study.
Figure 2. Meta-analysis of PBSO and breast cancer risk in BRCA1 or BRCA2 mutation carriers. A, PBSO and breast cancer risk in BRCA1/2 mutation carriers. B, PBSO and breast cancer risk in BRCA1 mutation carriers. C, PBSO and breast cancer risk in BRCA2 mutation carriers. The width of the horizontal line represents the 95% CI of the individual study, and the square proportional represents the weight of each study. The weight was calculated by the sample size of each individual study, and was presented by the percentage of total. The diamond represents the pooled RR and 95% CI. BC, breast cancer.
of post-BPM breast cancer in cases corresponds to a RR of 0.114 (95% CI, 0.041–0.317), confirming a substantial and statistically significant reduction in breast cancer risk after BPM in BRCA1/2 mutation carriers (Table S2, Figure 3A). Based on data from 4 nonoverlapping studies (13, 22, 23, 34), which included 1,269 participants, BPM significantly decreased the incidence of breast cancer (summary RR, 0.134; 95% CI, 0.019–0.937) in BRCA1 mutation carriers (Table S2). Finally, based on data from the same 4 nonoverlapping studies (13, 22, 23, 34), which included 783 participants, BPM significantly decreased the incidence of breast cancer (summary RR, 0.183; 95% CI, 0.072–0.468) in BRCA2 mutation carriers (Table S2).

**CPM and CBC risk.** For the analyses of CPM and CBC risk in BRCA1/2 mutation carriers, 4 nonoverlapping studies (11, 14–16) were included, which included 1,672 participants. CPM significantly decreased the incidence of CBC in BRCA1/2 mutation carriers (summary RR, 0.072; 95% CI, 0.035–0.148; Table S3, Figure 3B). No study estimated the risk reduction associated with CPM separately in BRCA1 and BRCA2 mutation carriers.

**Prophylactic surgery and mortality**

**PBSO and mortality.** Mortality reduction following PBSO was estimated separately in different scenarios incorporating mutation type (BRCA1 or BRCA2) and breast cancer history (prior history of breast cancer or none).

**PBSO and mortality in those with no prior history of breast cancer.** Two nonoverlapping studies (22, 23) were included in the meta-analysis of PBSO and mortality in BRCA1/2 mutation carriers with
no prior history of breast cancer. PBSO was associated with significantly lower all-cause mortality (summary HR, 0.349; 95% CI, 0.190–0.639) (Table 3 and Figure 4A). One study carried out by Domchek and colleagues (23) analyzed the association stratified by mutation status. It reported that all-cause mortality in BRCA1 mutation carriers was not statistically significant (HR, 0.52; 95% CI, 0.24–1.14). No study researched the relationship between mortality and PBSO in BRCA2 mutation carriers without prior history of breast cancer.

Besides, Domchek and colleagues (23) demonstrated that breast cancer-specific mortality reduction was not statistically significant in BRCA1/2 mutation carriers with no prior breast cancer (HR, 0.27; 95% CI, 0.05–1.33), neither in BRCA1 mutation carriers (HR, 0.30; 95% CI, 0.06–1.53).

**PBSO and mortality in those with prior history of breast cancer.** Four nonoverlapping studies (11, 15, 16, 23) were included in the meta-analysis of PBSO and mortality in BRCA1/2 mutation carriers with prior breast cancer. PBSO was associated with a significantly lower all-cause mortality in BRCA1/2 mutation carriers (summary HR, 0.432; 95% CI, 0.318–0.588; Table 3, Figure 4B), as well as breast cancer–specific mortality (summary HR, 0.337; 95% CI, 0.190–0.598; Table 3).

When analyzed by mutation status, Domchek and colleagues (23) demonstrated that PBSO was associated with a significantly lower all-cause mortality (HR, 0.26; 95% CI, 0.13–0.52) and breast cancer–specific mortality (HR, 0.27; 95% CI, 0.12–0.58) in BRCA1 mutation carriers. With fewer participants and fewer events, all-cause mortality (HR, 0.45; 95% CI, 0.17–1.16) and breast cancer–specific mortality (HR, 0.87; 95% CI, 0.32–2.37) in BRCA2 mutation carriers was not reduced statistically significantly.

**BPM and mortality.** Two eligible nonoverlapping articles (13, 22) examined the association of BPM and mortality among BRCA1/2 mutation carriers with no prior history of cancer. BPM was not significantly associated with reduced all-cause mortality (summary HR, 0.226; 95% CI, 0.05–1.016; Table 3, Figure 4A). Heemskerk-Gerritsen and colleagues (13) found that breast cancer–specific mortality was also not significantly reduced, giving a HR of 0.29 (95% CI, 0.03–2.61).

**CPM and mortality.** Four nonoverlapping articles (11, 14–16) were eligible examining the association of CPM and all-cause mortality among BRCA1/2 mutation carriers with unilateral breast cancer (UBC). All-cause mortality was significantly lower for patients with CPM than for those without CPM (summary HR, 0.512; 95% CI, 0.368–0.714; Table 3, Figure 5B). Besides, a study carried out by van Sprundel and colleagues (11) showed that breast cancer–specific survival was not significantly better in the CPM group (log rank, P = 0.11). Another study carried out by Metcalfe and colleagues (15) showed that CPM was significantly associated with reduced breast cancer–specific mortality for the entire 20-year study period of follow-up (HR, 0.52; 95% CI, 0.29–0.93), but not significantly associated for the first 10 years of follow-up (HR, 0.65; 95% CI, 0.34–1.22).

Obviously, the combination of PBSO and CPM gave the best overall survival. Having opted for both CPM and PBSO resulted in a significantly better survival than surveillance only (all-cause mortality summary HR, 0.145; 95% CI, 0.065–0.324), based on data from two eligible articles (11, 16; Table 3).

**Publication bias.** We found no evidence of publication bias in any analyses using Begg or Egger tests (all P > 0.05).

**Discussion**

This is, to the best of our knowledge, the first study that systematically investigated the most appropriate prophylactic surgery of breast cancer in BRCA1/2 mutation carriers. We have
summarized the evidence for prophylactic surgeries of breast cancer risk and mortality in women who have inherited *BRCA1* or *BRCA2* mutations.

The results of this meta-analysis suggest a 45% reduction in breast cancer risk, and a 65% reduction in all-cause mortality associated with PBSO in women who carry *BRCA1/2* mutation with no prior history of breast cancer. And PBSO was associated with a 57% reduction in all-cause mortality in breast cancer patients. All the available data may demonstrate the utility of PBSO in this population of patients. However, previous studies reported that 90% of invasive breast cancers found in *BRCA1* mutation carriers were estrogen receptor (ER) and progesterone receptor (PR) negative (35–37). And tumors associated with *BRCA2* mutations tend to be ER and PR positive (38). So, it is critical to understand how risk reduction may differ by gene. The prospective cohort study carried out by Kauff and colleagues (20) demonstrated that PBSO may be associated with a greater reduction in breast cancer risk in *BRCA2* mutation carriers than in *BRCA1* mutation carriers. However, the retrospective cohort study (19) and case-control study (17) did not observe this difference. Similarly, we did not observe this difference in our meta-analysis. To date, limited studies have been reported on the survival benefit of PBSO separately by gene; no meta-analysis could be performed. Domchek and colleagues (23) demonstrated in a prospective cohort study that PBSO was associated with a significantly lower all-cause mortality and breast cancer-specific mortality in *BRCA1* mutation carriers, but not significantly in *BRCA2* mutation carriers with prior history of breast cancer. Meanwhile, they found that all-cause mortality in *BRCA1* mutation carriers with no prior history of breast cancer was not reduced significantly. It is supposed that differences in study design, small sample size, and short period of follow-up time may influence the inferences we can make about the differences in risk reduction associated with PBSO in *BRCA1* versus *BRCA2* mutation carriers. And others suggested that PBSO might inhibit breast cancer growth in *BRCA1* mutation carriers at tumorigenesis: growth of ER- and PR-negative cells might be indirectly induced paracrine signals from ER- and PR-positive cells that are influenced by estrogen and progesterone. It is also supposed that...
PBSO exerts more than just an antiestrogenic effect. Definitely, the mechanism of action of PBSO in BRCA1 mutation carriers is unclear and should be investigated further.

PM is considered to be the most effective strategy for reducing breast cancer risk. The results of this meta-analysis suggested that BPM was associated with a 90% reduction in breast cancer risk, and CPM was associated with a 93% reduction in CBC risk. It is clear that PM does not completely eliminate the breast cancer risk. There is still a residual risk of breast cancer after PM in BRCA1/2 mutation carriers. The potential mechanism requires further research. In addition, the results indicated that all-cause mortality rates were reduced by BPM, although significant survival benefits could not be claimed yet. However, CPM was found to be significantly associated with improved overall survival in BRCA1/2 mutation carriers with a history of UBC. Of note, CBCs were mostly diagnosed at a more favorable stage than PBCs, that is more DCIS, smaller tumor size and more node-negative breast cancer, which may be the result of accurate surveillance after PBC (14). Thus, the survival benefit of CPM cannot completely be explained by the prevention of CBC-associated deaths. However, despite a relatively lower CBC stage, it is suggested that survival of sporadic bilateral breast cancer is worse than survival of UBC patients (39, 40). Whether this difference could apply for BRCA1/2 mutation carriers is not clear yet, and should be investigated further.

All in all, the meta-analysis and systematic review provide an up-to-date analysis of the advantages of prophylactic surgeries in BRCA1/2 mutation carriers. However, selecting the most appropriate prophylactic strategy is not a straightforward task. Prophylactic surgeries may ensure a very high protection from breast cancer, but are associated with a number of disadvantages of invasiveness, nonreversibility, and surgical morbidity. PBSO could cause menopause with its attendant symptoms, increase in heart disease and osteoporosis risk, and for some women a loss of sexuality and gender identity (41–43). PM may even have a greater impact psychologically than PBSO because it affects body image. Parting with a healthy breast (or two) to prevent a probability is very difficult, which may result
in anxiety, lack of self-esteem, and possibly depression. However, the decision to undergo prophylactic surgery is an individual and personal choice that a woman has to make together with her doctor.

In a meta-analysis of the literature, we must always bear in mind that results are based on the findings of completed studies. As a result, there are some limitations in the present meta-analysis. First, to date, comparative data on the advantage of prophylactic surgery among BRCA1/2 mutation carriers are limited. Limitations of the currently available data regarding prophylactic surgery in BRCA1/2 mutation carriers include variable study designs, small sample size for some studies, variable patients’ age, and so on. Of note, a case–control design study was included in the summary estimates, which yielded ORs rather than HRs. Although ORs may slightly overestimate the risk reduction associated with PBSO, the annual incidence of breast cancer in BRCA1/2 mutation carriers is no more than 2% to 4%, with the result that ORs are likely to be similar to HRs in this setting. Second, though HRs of included studies are all adjusted by acknowledged relevant factors to ensure relative reliability, some reported studies use different adjustments for potential confounder variables. The inconsistent use of adjustment and matching factors may further limit the comparability of studies, and may have resulted in varying levels of confounding across studies. In addition, crude RR with 95% CI was used to assess the association between BPM and breast cancer risk, and the association between CPM and CBC risk. Because of the insufficient information provided by the original articles, it is impossible to calculate weighted pooled estimates. Moreover, no adjusted RR was presented in most of these articles. As a result, we could only calculate crude RR through data extracted from these articles. A third limitation concerns the small numbers of BRCA2 mutation carriers in most studies investigating the survival benefit of prophylactic surgery, so that analyzing the data separately for BRCA1 and BRCA2 mutation carriers was not possible. Fourth, the age at prophylactic surgery and the follow-up periods for participants have differed between studies eligible in the meta-analysis. Thus, the effect of age at prophylactic surgery on breast cancer risk and mortality reduction remains unresolved. And for short follow-up times in some studies, a delay in the risk and mortality reduction remains unresolved. And for short follow-up times in some studies, a delay in the risk and mortality reduction remains unresolved. Consequently, a conservative attitude should be held towards the conclusions. Finally, ideally, the evaluation of prophylactic surgery on cancer risk and mortality reduction would involve a randomized trial design. However, there are no randomized controlled trials concerned with the demonstration of the potential benefits or harms of prophylactic surgery currently, for that it is accepted in the field that a randomized approach would neither be acceptable nor ethical.

Conclusions

In conclusion, options to reduce the high breast cancer incidence and mortality risk include PBSO and PM (BPM and CPM). The summary risk reduction estimates presented in our meta-analysis confirm that BRCA1/2 mutation carriers who have been treated with prophylactic surgery have a substantially reduced risk of breast cancer and mortality. This meta-analysis and systematic review could serve as a helpful guide for clinicians during the discussion with their patients before the final prophylactic surgical decision is made. However, further prospective studies with larger sample size and longer follow-up periods are still required to get a more precise estimation of the benefits and potential harms of prophylactic surgeries among BRCA1 or BRCA2 mutation carriers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: X. Li, C. Liu, Z. Xu, B. Yu, T. Xu, H. Cai
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): X. Li, C. Liu
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): X. Li, B. Yu
Writing, review, and/or revision of the manuscript: X. Li, R. You, X. Wang, C. Liu, B. Yu, H. Cai
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H. Cai, Q. Zou
Study supervision: Z. Xu, T. Xu, H. Cai, Q. Zou

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References


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