Association of Risk-Reducing Surgery in BRCA1 or BRCA2 Mutation Carriers With Cancer Risk and Mortality

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Women who have inherited mutations in the BRCA1 or BRCA2 (BRCA1/2) genes have substantially elevated risks of breast cancer and ovarian cancer, with a lifetime risk of breast cancer of 56% to 84%.1-3 The estimated ovarian cancer risks range from 36% to 63% for BRCA1 mutation carriers and 10% to 27% for BRCA2 mutation carriers.1-6

Context Mastectomy and salpingo-oophorectomy are widely used by carriers of BRCA1 or BRCA2 mutations to reduce their risks of breast and ovarian cancer.

Objective To estimate risk and mortality reduction stratified by mutation and prior cancer status.

Design, Setting, and Participants Prospective, multicenter cohort study of 2482 women with BRCA1 or BRCA2 mutations ascertained between 1974 and 2008. The study was conducted at 22 clinical and research genetics centers in Europe and North America to assess the relationship of risk-reducing mastectomy or salpingo-oophorectomy with cancer outcomes. The women were followed up until the end of 2009.

Main Outcomes Measures Breast and ovarian cancer risk, cancer-specific mortality, and overall mortality.

Results No breast cancers were diagnosed in the 247 women with risk-reducing mastectomy compared with 98 women of 1372 diagnosed with breast cancer who did not have risk-reducing mastectomy. Compared with women who did not undergo risk-reducing salpingo-oophorectomy, women who underwent salpingo-oophorectomy had a lower risk of ovarian cancer, including those with prior breast cancer (6% vs 1%, respectively; hazard ratio [HR], 0.14; 95% confidence interval [CI], 0.04-0.59) and those without prior breast cancer (6% vs 2%; HR, 0.28 [95% CI, 0.12-0.69]), and a lower risk of first diagnosis of breast cancer in BRCA1 mutation carriers (20% vs 14%; HR, 0.63 [95% CI, 0.41-0.96]) and BRCA2 mutation carriers (23% vs 7%; HR, 0.36 [95% CI, 0.16-0.82]). Compared with women who did not undergo risk-reducing salpingo-oophorectomy, undergoing salpingo-oophorectomy was associated with lower all-cause mortality (10% vs 3%; HR, 0.40 [95% CI, 0.26-0.61]), breast cancer-specific mortality (6% vs 2%; HR, 0.44 [95% CI, 0.26-0.76]), and ovarian cancer-specific mortality (3% vs 0.4%; HR, 0.21 [95% CI, 0.06-0.80]).

Conclusions Among a cohort of women with BRCA1 and BRCA2 mutations, the use of risk-reducing mastectomy was associated with a lower risk of breast cancer; risk-reducing salpingo-oophorectomy was associated with a lower risk of ovarian cancer, first diagnosis of breast cancer, all-cause mortality, breast cancer-specific mortality, and ovarian cancer-specific mortality.

JAMA. 2010;304(9):967-975

For editorial comment see p 1011.

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a history of breast cancer may differ and be of clinical relevance. Likewise, data are emerging that suggest BRCA1 mutation carriers may experience differential benefits from interventions such as salpingo-oophorectomy compared with BRCA2 mutation carriers.15,17 Herein, we examine a large cohort of BRCA1/2 mutation carriers followed up prospectively and report cancer risk-reduction estimates following risk-reducing salpingo-oophorectomy and risk-reducing mastectomy in a number of scenarios incorporating mutation type (BRCA1 vs BRCA2), and cancer history (prior history of breast cancer vs none).

METHODS
Women with inherited, disease-associated BRCA1/2 mutations were identified from 22 centers in the Prevention and Observation of Surgical Endpoints (PROSE) consortium. Participants were ascertained between 1974 and 2008. The PROSE protocol was previously described.15 All participants underwent an informed consent process for participation in research. This protocol was approved by the institutional review board at each institution. Study participants were enrolled as a cohort with time of follow-up starting from patient ascertainment into the research program. Genetic testing was performed per institutional guidelines and all patients received posttest counseling to review management options. Women who declined risk-reducing salpingo-oophorectomy or mastectomy were offered increased surveillance at all centers according to established guidelines. At US sites, this consisted of annual mammography and magnetic resonance imaging for those with breast tissue, and transvaginal ultrasound every 6 to 12 months and CA 125 blood testing for those with ovaries in place. In the United Kingdom, women were offered annual mammography and magnetic resonance imaging until age 50 years. Ovarian cancer screening consisted of transvaginal ultrasonography and CA 125 blood testing every 4 months.

Patients were eligible for the study if they had no prior ovarian cancer diagnosis and no salpingo-oophorectomy at the time of ascertainment and had a minimum of 6 months of follow-up. Patients were excluded if they received a cancer diagnosis within the first 6 months of follow-up (to avoid including cancers that would have been minimally influenced by risk-reducing salpingo-oophorectomy or mastectomy). Participants were followed up until the end of 2009. The median follow-up was 3.65 years (range, 0.52–27.4 years) among those who underwent surgery and 4.29 years (range, 0.5–27.9 years) in women who did not undergo surgery.

There were 4255 known BRCA1/2 mutation carriers in the PROSE study that were considered for inclusion. Twelve women were excluded because they had both BRCA1 and BRCA2 mutations, 325 because they underwent salpingo-oophorectomy before the ascertainment date, 363 because they were diagnosed with ovarian cancer before the ascertainment date, 738 because they had been followed up for less than 6 months, and 135 because they had incident cases of cancer. Participants who had undergone risk-reducing mastectomy prior to ascertainment were excluded from all breast cancer incidence analyses. Breast cancer included invasive cancers and ductal carcinoma in situ.

Women who had not undergone risk-reducing mastectomy were followed up prospectively from the age at ascertainment. Women who had undergone risk-reducing mastectomy after ascertainment were followed up from the age at the time of their risk-reducing mastectomy. The primary outcome was breast cancer. If no breast cancer occurred, women were censored at the age of ovarian cancer diagnosis, death, or last contact.

Women who underwent risk-reducing salpingo-oophorectomy after ascertainment were followed up from the age at the time of their salpingo-oophorectomy. Women who had not undergone risk-reducing salpingo-oophorectomy were followed up prospectively from the age at ascertainment. The outcomes of interest were ovarian cancer diagnosis, breast cancer diagnosis, second diagnosis of primary breast cancer, and mortality.

For ovarian cancer end points, women were followed up until ovarian cancer diagnosis, censoring at death, or last contact. Women were excluded if they were diagnosed with an occult ovarian cancer during risk-reducing salpingo-oophorectomy. When missing data were encountered, the individual was dropped from the analysis that involved the missing data point, but the individual was included in other analyses in which complete data were available; in fact, because many of the data items were required for enrollment, missing data was only applicable to ovarian cancer end points. For breast cancer end points, women were excluded if they underwent risk-reducing mastectomy prior to ascertainment. Women who had risk-reducing mastectomy after ascertainment but before risk-reducing salpingo-oophorectomy were considered unexposed and were censored at the time of risk-reducing mastectomy. Women were followed up until breast cancer diagnosis or were censored at the time of ovarian cancer diagnosis, risk-reducing mastectomy, death, or last contact. For analysis of second diagnosis of primary breast cancer, the aforementioned censoring criteria were applied, and women also were censored at the time of a contralateral mastectomy. A second diagnosis of breast cancer was defined as any contralateral breast cancer or an ipsilateral breast cancer diagnosed more than 5 years after the first.

For the mortality analysis, the inclusion and follow-up methods were similar to the salpingo-oophorectomy analyses described above. However, women were censored at last contact, with the primary outcome being death.

The effects of risk-reducing salpingo-oophorectomy and risk-reducing mastectomy on cancer incidence and mortality were analyzed using Cox proportional hazards models. A robust variance-covariance esti-
Risk-reducing salpingo-oophorectomy was associated with a decreased risk of ovarian cancer. Among those with no prior breast cancer, the risk reduction in BRCA1 mutation carriers was a HR of 0.15 (95% confidence interval [CI], 0.04-0.63). No cases of ovarian cancer were diagnosed in BRCA2 mutation carriers. In the 6 years of prospective follow-up, 3% of women without salpingo-oophorectomy over a similar follow-up period were diagnosed with ovarian cancer. Among those with prior diagnosis of breast cancer, the risk reduction in BRCA1 mutation carriers was an HR of 0.15 (95% CI, 0.04-0.63). No cases of ovarian cancer were diagnosed in BRCA2 mutation carriers. In contrast, 3% of women without salpingo-oophorectomy over a similar follow-up period were diagnosed with ovarian cancer. Among women with prior diagnosis of breast cancer who underwent risk-reducing salpingo-oophorectomy before the age of 50 years (HR, 1.36; 95% CI, 0.26-7.05). The test for interaction yielded an HR of 0.62 (95% CI, 0.41-0.95; P = .03). In BRCA1 and BRCA2 mutation carriers with a prior diagnosis of breast cancer, there was no evidence for reduction in risk of a second diagnosis of primary breast cancer.

Salpingo-oophorectomy was associated with significantly lower all-cause mortality in those with no prior breast cancer (HR, 0.43; 95% CI, 0.21-0.95) and those with prior breast cancer (HR, 0.30 [95% CI, 0.17-0.52]; Table 4).
When analyzed by mutation status, salpingo-oophorectomy was associated with a significantly lower all-cause mortality in BRCA1 mutation carriers overall (HR, 0.38; 95% CI, 0.24-0.62). With fewer participants and fewer events, all-cause mortality in BRCA2 mutation carriers was not statistically significant (HR, 0.52; 95% CI, 0.22-1.23).

Table 2. Risk-Reducing Salpingo-oophorectomy and Ovarian Cancer Risk

<table>
<thead>
<tr>
<th>Prior Breast Cancer</th>
<th>Risk-reducing salpingo-oophorectomy</th>
<th>Total (n = 1557)</th>
<th>BRCA1 (n = 1003)</th>
<th>BRCA2 (n = 554)</th>
<th>Total (n = 1060)</th>
<th>BRCA1 (n = 684)</th>
<th>BRCA2 (n = 376)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>465 (29.9)</td>
<td>342 (34.1)</td>
<td>123 (22.2)</td>
<td>474 (44.7)</td>
<td>339 (49.6)</td>
<td>135 (35.9)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1092 (70.1)</td>
<td>661 (65.9)</td>
<td>431 (77.8)</td>
<td>586 (55.3)</td>
<td>345 (50.4)</td>
<td>241 (64.1)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 3. Risk-Reducing Salpingo-oophorectomy and Breast Cancer Risk

<table>
<thead>
<tr>
<th>Prior Breast Cancer</th>
<th>Risk-reducing salpingo-oophorectomy</th>
<th>Total (n = 1370)</th>
<th>BRCA1 (n = 889)</th>
<th>BRCA2 (n = 501)</th>
<th>Total (n = 847)</th>
<th>BRCA1 (n = 397)</th>
<th>BRCA2 (n = 250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>336 (24.5)</td>
<td>236 (27.2)</td>
<td>100 (20.0)</td>
<td>208 (32.1)</td>
<td>138 (34.8)</td>
<td>70 (28.0)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1034 (75.5)</td>
<td>633 (72.8)</td>
<td>401 (80.0)</td>
<td>439 (67.9)</td>
<td>259 (65.2)</td>
<td>180 (72.0)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.
Salpingo-oophorectomy was associated with a lower breast cancer–specific mortality (HR, 0.44 [95% CI, 0.26-0.76]; Table 5) and ovarian cancer–specific mortality (HR, 0.21 [95% CI, 0.06-0.80]; Table 6). In BRCA1 mutation carriers, salpingo-oophorectomy was associated with improved breast cancer–specific mortal-

### Table 4. Risk-Reducing Salpingo-oophorectomy and All-Cause Mortality

<table>
<thead>
<tr>
<th>Risk-reducing salpingo-oophorectomy</th>
<th>All Eligible Women</th>
<th>No Prior Breast Cancer</th>
<th>Prior Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 2482)</td>
<td>BRCA1 (n = 1587)</td>
<td>BRCA2 (n = 895)</td>
<td>Total (n = 1458)</td>
</tr>
<tr>
<td>Deaths</td>
<td>31 (3.1)</td>
<td>25 (3.5)</td>
<td>6 (2.1)</td>
</tr>
<tr>
<td>No</td>
<td>1489 (60.0)</td>
<td>881 (55.5)</td>
<td>608 (67.9)</td>
</tr>
</tbody>
</table>

#### Follow-up, mean (range), y

- **Age, mean (range), y**
  - At time of oophorectomy: 45.4 (20.5-79.0)
  - At start of follow-up for those without oophorectomy: 39.8 (18.1-90.4)

- **Follow-up, mean (range), y**
  - To death: 6.0 (0.5-23.5)
  - To censoring: 5.0 (0.5-27.9)

- **All-cause mortality after risk-reducing salpingo-oophorectomy, HR (95% CI)**
  - Age <50 y: 0.40 (0.26-0.61)
  - Age ≥50 y: 0.37 (0.15-0.94)

### Table 5. Risk-Reducing Salpingo-oophorectomy and Breast Cancer–Specific Mortality

<table>
<thead>
<tr>
<th>Risk-reducing salpingo-oophorectomy</th>
<th>All Eligible Women</th>
<th>No Prior Breast Cancer</th>
<th>Prior Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 2407)</td>
<td>BRCA1 (n = 1536)</td>
<td>BRCA2 (n = 871)</td>
<td>Total (n = 1414)</td>
</tr>
<tr>
<td>Deaths</td>
<td>21 (2.1)</td>
<td>16 (2.3)</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>No</td>
<td>1424 (59.2)</td>
<td>839 (54.6)</td>
<td>585 (67.2)</td>
</tr>
</tbody>
</table>

#### Age, mean (range), y

- At time of oophorectomy: 45.3 (20.5-75.2)
- At start of follow-up for those without oophorectomy: 39.3 (18.1-87.6)

- **Follow-up, mean (range), y**
  - To death: 4.6 (0.5-21.4)
  - To censoring: 5.0 (0.5-27.9)

- **Breast cancer–specific mortality after risk-reducing salpingo-oophorectomy, HR (95% CI)**
  - Age <50 y: 0.44 (0.26-0.76)
  - Age ≥50 y: 0.38 (0.20-0.72)

Abbreviations: CI, confidence interval; HR, hazard ratio.

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(Reprinted) JAMA, September 1, 2010—Vol 304, No. 9 971
ity (HR, 0.38 [95% CI, 0.20-0.72]; Table 5) and ovarian cancer–specific mortality (HR, 0.22 [95% CI, 0.06-0.83]; Table 6). There were neither ovarian cancer deaths following salpingo-oophorectomy in BRCA2 mutation carriers, nor were there any breast cancer deaths in BRCA2 mutation carriers who underwent salpingo-oophorectomy prior to cancer diagnosis. In an exploratory analysis, overall survival was associated with salpingo-oophorectomy in those younger than 50 years (HR, 0.41; 95% CI, 0.25-0.67) and in those aged 50 years or older (HR, 0.37; 95% CI, 0.15-0.94) (Table 4); however, a test of interaction was not significant, which suggests no difference in overall mortality benefit between these 2 groups.

There have been 8 deaths after salpingo-oophorectomy in those without cancer prior to salpingo-oophorectomy: 2 of the deaths were from breast cancer and 3 deaths were primary peritoneal cancer (1 due to leukemia, 1 due to stomach cancer, and 1 death that was not related to cancer; eTable 1 and eTable 2 at http://www.jama.com). Although 151 women without prior cancer also underwent mastectomy (34%), neither of the 2 who died from breast cancer had undergone risk-reducing mastectomy. In those patients with breast cancer prior to salpingo-oophorectomy, 23 died (including 19 deaths due to breast cancer and 1 due to ovarian cancer).

**COMMENT**

The clinical management of cancer risk in BRCA1 and BRCA2 mutation carriers is complex and is best informed by accurate knowledge of the outcomes of interventions. Most prior studies that have investigated the effect of risk-reducing salpingo-oophorectomy or mastectomy on breast cancer risk did not examine effects either by mutation status or by prior cancer diagnosis. There may be little added benefit of risk-reducing salpingo-oophorectomy on breast cancer risk if women have chemotherapy-induced menopause, or if they are already receiving hormonal therapy. We hypothesize that both of these factors are important in determining precise estimates of risk reduction. Our results confirm that risk-reducing mastectomy is associated with a significant reduction in breast cancer risk. In addition, risk-reducing salpingo-oophorectomy is associated with a significant decrease in ovarian cancer risk in both BRCA1 and BRCA2 mutation carriers, and in those with and without a prior diagnosis of breast cancer. There is a significant reduction in breast cancer risk following risk-reducing salpingo-oophorectomy in both BRCA1 and BRCA2 mutation carriers without prior cancer diagnosis. Overall mortality was improved in women undergoing risk-reducing salpingo-oophorectomy. In women who underwent risk-reducing salpingo-oophorectomy, 1.1% were subsequently diagnosed with ovarian cancer, 11.4% were subsequently diagnosed with breast cancer, and 3.1% subsequently died of any cause. In women who did not undergo risk-reducing salpingo-oophorectomy, 5.8% were subsequently diagnosed with ovarian cancer, 19.2% with breast cancer, and 9.8% subsequently died from any cause.

Risk-reducing mastectomy is a highly effective strategy for breast cancer risk reduction. In our prospec-

### Table 6. Risk-Reducing Salpingo-oophorectomy and Ovarian Cancer–Specific Mortality

<table>
<thead>
<tr>
<th>Total (n = 2343)</th>
<th>BRCA1 (n = 1502)</th>
<th>BRCA2 (n = 841)</th>
<th>Total (n = 1417)</th>
<th>BRCA1 (n = 907)</th>
<th>BRCA2 (n = 510)</th>
<th>Total (n = 2928)</th>
<th>BRCA1 (n = 1570)</th>
<th>BRCA2 (n = 1358)</th>
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<tbody>
<tr>
<td>Risk-reducing salpingo-oophorectomy</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>966 (41.2)</td>
<td>685 (45.6)</td>
<td>281 (33.4)</td>
<td>442 (31.2)</td>
<td>322 (35.5)</td>
<td>120 (23.5)</td>
<td>433 (46.7)</td>
<td>304 (50.9)</td>
</tr>
<tr>
<td>Deaths</td>
<td>4 (0.4)</td>
<td>4 (0.6)</td>
<td>0</td>
<td>3 (0.7)</td>
<td>3 (0.9)</td>
<td>0</td>
<td>1 (0.2)</td>
<td>1 (0.3)</td>
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<tr>
<td>No</td>
<td>1377 (58.8)</td>
<td>817 (54.4)</td>
<td>560 (66.6)</td>
<td>580 (25.5)</td>
<td>322 (35.5)</td>
<td>390 (76.5)</td>
<td>495 (46.7)</td>
<td>293 (49.9)</td>
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<tr>
<td>Deaths</td>
<td>34 (2.5)</td>
<td>29 (3.5)</td>
<td>5 (0.9)</td>
<td>24 (2.5)</td>
<td>20 (3.4)</td>
<td>4 (1.0)</td>
<td>11 (2.2)</td>
<td>10 (3.4)</td>
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<tr>
<td>Age, mean (range), y</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>At time of oophorectomy</td>
<td>45.3</td>
<td>44.4</td>
<td>47.4</td>
<td>43.2</td>
<td>42.0</td>
<td>46.4</td>
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<td>(20.5-75.2)</td>
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<td>At start of follow-up for those without oophorectomy</td>
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<tr>
<td>39.5</td>
<td>38.2</td>
<td>41.3</td>
<td>36.1</td>
<td>34.8</td>
<td>38.0</td>
<td>45.6</td>
<td>44.4</td>
<td>47.3</td>
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<td>(18.1-87.9)</td>
<td>(18.2-87.9)</td>
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<td>(18.1-87.9)</td>
<td>(21.9-86.2)</td>
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<td>Follow-up, mean (range), y</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>To death</td>
<td>8.4</td>
<td>8.7</td>
<td>6.9</td>
<td>8.8</td>
<td>9.1</td>
<td>7.0</td>
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<td>(1.4-22.3)</td>
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<td>(5.2-9.0)</td>
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<td>(5.2-9.0)</td>
<td>(5.2-9.0)</td>
<td>(2.8-18.7)</td>
</tr>
<tr>
<td>To censoring</td>
<td>5.0</td>
<td>5.0</td>
<td>4.9</td>
<td>5.8</td>
<td>5.7</td>
<td>5.9</td>
<td>4.5</td>
<td>4.8</td>
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<tr>
<td>(0.5-27.8)</td>
<td>(0.5-27.7)</td>
<td>(0.5-27.9)</td>
<td>(0.5-27.9)</td>
<td>(0.5-27.9)</td>
<td>(0.5-27.9)</td>
<td>(0.5-27.9)</td>
<td>(0.5-27.9)</td>
<td>(0.5-26.4)</td>
</tr>
<tr>
<td>Ovarian cancer–specific mortality after risk-reducing salpingo-oophorectomy, HR (95% CI)</td>
<td>0.21</td>
<td>0.22</td>
<td>No deaths</td>
<td>No deaths</td>
<td>No deaths</td>
<td>No deaths</td>
<td>No deaths</td>
<td>No deaths</td>
</tr>
<tr>
<td>(0.06-0.80)</td>
<td>(0.06-0.83)</td>
<td>(0.01-1.44)</td>
<td>(0.01-1.44)</td>
<td>(0.01-1.44)</td>
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<td>(0.01-1.44)</td>
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<td>(0.01-1.44)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, range not available because there was only 1 observation.

*Values are expressed as number (percentage) unless otherwise indicated. Participants were censored at last contact.

There were no cases of breast cancer prior to risk-reducing salpingo-oophorectomy or in those who did not undergo salpingo-oophorectomy prior to the start of follow-up.

Breast cancer allowed prior to risk-reducing salpingo-oophorectomy or start of follow-up.

Adjusted for year of birth, oral contraceptive use, and stratified by center.
Before risk-reducing mastectomy. The observation of no prospectively identified breast cancer cases may be due to biases in prior retrospective studies or improved surgical techniques in recent prospective analyses.

Risk-reducing salpingo-oophorectomy is highly effective in reducing ovarian and fallopian tube cancers in both BRCA1 and BRCA2 mutation carriers and in those with and without prior breast cancer. Precise estimates of risk reduction following risk-reducing salpingo-oophorectomy are needed to balance the increasingly recognized health risks caused by premature menopause. We observed no primary peritoneal cancers following risk-reducing salpingo-oophorectomy in BRCA2 mutation carriers, although such cancers have been reported. In BRCA1 mutation carriers, risk-reducing salpingo-oophorectomy was associated with a 70% reduction in the risk of ovarian cancer in those without prior breast cancer and an 85% reduction in those with prior breast cancer. It is unknown whether these numbers are truly different, reflect censoring from death due to breast cancer, or are a protective effect following breast cancer treatment.

Risk-reducing salpingo-oophorectomy was associated with a significantly decreased risk of breast cancer in those without prior breast cancer with both BRCA1 (37% reduction) and BRCA2 mutations (64% reduction). In mutation carriers with prior breast cancer, risk-reducing salpingo-oophorectomy had no effect on risk of second diagnosis of primary breast cancer. In women with sporadic breast cancer, the benefit of risk-reducing salpingo-oophorectomy when added to standard adjuvant treatment is uncertain and is the subject of multiple ongoing clinical trials. Chemotherapy often leads to cessation of menses, so any effect of ovarian ablation from risk-reducing salpingo-oophorectomy may be achieved in some women by chemotherapy. In premenopausal women with estrogen receptor (ER)-positive tumors, hormone therapy in addition to chemotherapy significantly improves disease-free survival. Our data are in contrast to prior reports demonstrating benefit of oophorectomy in preventing contralateral breast cancer. Differences in adjuvant therapy use could explain these discrepancies; however, a limitation of our study is the absence of detailed treatment information. It is important to note that ovarian cancer risk is independent of menopause; menopause either naturally occurring or chemotherapy-induced is not known to decrease the risk of ovarian cancer. Regardless of the effect of oophorectomy on second diagnosis of breast cancer, oophorectomy is essential to reduce the risk of ovarian cancer, which can be a significant cause of morbidity and mortality in women with early-stage breast cancer.

Our data suggest that risk-reducing salpingo-oophorectomy may be associated with a lower breast cancer risk in BRCA2 mutation carriers than in BRCA1 mutation carriers (64% vs 37%, respectively). Kauf et al observed a statistically significant breast cancer risk reduction following risk-reducing salpingo-oophorectomy in BRCA2 but not BRCA1 mutation carriers. The potentially larger risk reduction associated with risk-reducing salpingo-oophorectomy in BRCA2 compared with BRCA1 mutation carriers is of interest given the high proportion of ER-positive breast tumors in BRCA2 mutation carriers compared with BRCA1 mutation carriers. Additional research is required to address this issue.

We are still unable to provide definitive data with respect to the timing of risk-reducing salpingo-oophorectomy on the efficacy of breast cancer risk reduction because the numbers in each subgroup remain small with a limited number of events. Eisen et al reported that the breast cancer risk reduction with salpingo-oophorectomy was greater in BRCA1/2 mutation carriers who underwent surgery before the age of 50 years than in women who underwent surgery after the age of 50 years. The results of the present analyses are consistent with this finding for unaffected women who undergo risk-reducing salpingo-oophorectomy before age 50 years.

The importance of understanding the optimal age to undergo risk-reducing salpingo-oophorectomy is underscored by several reports in the general population that suggest that oophorectomy in women younger than age 45 years is associated with increased mortality, particularly if hormone therapy is not used. Although these data are not directly applicable to women with BRCA1/2 mutations who have markedly increased risks of breast and ovarian cancer and therefore a different risk and benefit profile, issues of timing and the safety of hormone therapy are important. The Women's Health Initiative in postmenopausal women did not demonstrate a cardiovascular benefit overall from hormone therapy, but younger women going through natural menopause may derive such benefit. It is possible that BRCA1/2 mutation carriers undergoing abrupt surgical menopause to reduce ovarian cancer risk and receive hormone therapy may derive health benefits. Two prior studies have examined hormone therapy in BRCA1/2 mutation carriers. Rebbeck et al examined 462 patients and reported no increased breast cancer risk with hormone therapy use after risk-reducing salpingo-oophorectomy. Eisen et al examined hormone therapy in women who had undergone risk-reducing salpingo-oophorectomy and observed no increased risk associated with hormone therapy use. Further work is needed regarding this important issue.

We observed an association of risk-reducing salpingo-oophorectomy with a significant reduction in all-cause, breast cancer–specific, and ovarian cancer–specific mortality. We previously reported that risk-reducing salpingo-oophorectomy was associated with a 90% reduction in breast cancer–specific mortality, a 95% reduction in ovarian cancer–specific mortality, and a 76% reduction in overall mortality. Our present estimates are consistent...
with those reports. The apparent lesser effect on mortality in BRCA2 vs BRCA1 mutation carriers may be due to the lower risk of ovarian cancer in BRCA2 mutation carriers as well as the more aggressive biological features of BRCA1-associated breast cancer; however, more data are needed to adequately address this important question.

There are a number of limitations to this study. We designed our study to maximize follow-up time and statistical power; however, this choice could have compromised our results in a number of ways. Our study design was powered to detect effects of risk-reducing salpingo-oophorectomy and mastectomy stratified on BRCA1/2 as well as the other groups defined in the tables. The observation of statistically significant P values in many strata provides evidence that we had sufficient power for our preplanned hypotheses. A few strata-specific analyses did not achieve statistical significance, suggesting that we did not have sufficient power to detect some smaller than anticipated effects. Therefore, analyses in some substra may require additional study after accrual of much larger sample sizes.

Ideally, the evaluation of risk-reducing surgery on cancer risk and mortality reduction would involve a randomized controlled trial design. However, it is accepted in the field that a randomized approach would neither be acceptable nor ethical. As a result, this field of research is limited to undertaking observational studies that have methodological limitations. An observational design requires that statistical methods be used to correct for factors that may influence relative risk estimates. We have attempted to correct for a number of limitations of the observational study design by using the recommended analysis approaches of Klaren et al.26 and Hartmann et al.27 However, additional analytical corrections could be considered in future analyses, including the effect of competing risks, or the consideration of the time-dependency aspect of risk-reducing salpingo-oophorectomy or risk-reducing mastectomy and other covariates. As a result of these limitations, our results cannot be assumed to be causal in nature.

Although all women who chose to forgo risk-reducing salpingo-oophorectomy were counseled to undergo intensive screening, we do not have detailed information on compliance of these recommendations at all centers. However, there are no data that ovarian cancer screening is effective in reducing the risk of developing ovarian cancer, or in reducing the risk of death from ovarian cancer.38 Therefore, we feel that it is unlikely that compliance would significantly alter our results related to the ovarian cancer end points of incidence and mortality. Intensive breast cancer surveillance does not reduce the risk of developing breast cancer, but aims to improve early detection. Due to our lack of detailed information on breast magnetic resonance imaging compliance, we cannot conclude that risk-reducing salpingo-oophorectomy improved breast cancer–specific mortality compared with optimal screening; however, we found an association between women who underwent risk-reducing salpingo-oophorectomy and women who have better outcomes in terms of breast cancer risk, ovarian cancer risk, and ovarian cancer–specific survival, none of which would be anticipated to be affected by compliance to intensive breast cancer screening. We also found an association between women who underwent risk-reducing salpingo-oophorectomy and breast cancer–specific and overall survival compared with women who have chosen to forgo risk-reducing salpingo-oophorectomy.

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Author Contributions: Dr Rebbeck had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Administrative, technical, or material support: Domchek, Friebel, Singer, Evans, Neuhaseain, Matloff, Eeles, Pichert, Van’t Veer, Tung, Weitzel, Couch, Ganz, Daly, Tomlinson, Schildkraut, Blum, Rebbeck.

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Financial Disclosures: None reported.

Funding/Support: This study was supported by grants RO1 CA83895 and RO1 CA102776 from the Public Health Service (awarded to Dr Rebbeck); funding from the University of Pennsylvania Cancer Center (awarded to Dr Rebbeck); grant HHSN21620074400C from the Cancer Genetics Network (awarded to Drs Domchek and Isaacs); funding from the Marjorie Cohen Research Fund (awarded to Dr Domchek); SPORE grant BC P50 CA-089393 from the Dana-Farber/Harvard Cancer Center (awarded to Dr Garber); grants DAMD-19-96-1-6088 (awarded to Andrew K. Godwin), DAMD-19-94-J-4340 and DAMD-19-97-J-7112 (awarded to Dr Lynch), and DAMD-19-93-J-0619 (awarded to Dr Domchek) from the US Department of Defense; grant P30-CA51008-15 (awarded to Georgetown University); funding from the Utah Cancer registry (which was funded by Public Health Service grant NO1-CN-6700) and the Utah State Department of Health; Nebraska State Cancer and Smoking-Related Diseases Research Program grants LB595 (awarded to Dr Lynch) and P30-CA-16042 (awarded to Dr Ganz); Cancer Research UK grants C5047/A7357 (awarded to Dr Eeles); and National Cancer Institute grant P30 CA51008-12 (awarded to...
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Dr Isaac). Dr Olopade receives funding as the Doris Duke Distinguished Clinical Scientist. Dr Elles received funding from the National Institute for Health Research (awarded to the Biomedical Research Centre at the Institute of Cancer Research and the Royal Marsden NHS Foundation Trust).

Role of the Sponsor: The sponsors had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

The PROSE Consortium includes the following individuals and centers. The number of participants who were included in the present study appears in the parentheses. Christian Singer, University of Vienna, Austria (n = 283); Nadine Tung, Beth Israel, Boston, Massachusetts (n = 119); Joanne L. Blum, Becky Althaus, Gabrielle Ethington, and Estelle Brothers, Baylor Charles A. Sammons Cancer Center (n = 13); Jeffrey Weitzel, City of Hope, Duarte, California (n = 98); Carli Snyder, Henry T. Lynch, and Patrice Watson, Creighton University, Omaha, Nebraska (n = 348); Katherine Corso, Kathryn Stockert, and Judy E. Garber, Dana-Farber Cancer Institute, Boston, Massachusetts (n = 311); Joellen Schildkraut, Duke University, Durham, North Carolina (n = 199); Wendy S. Rubinstein, Christina Selkirk, and Scott M. Weissman, NorthShore University HealthSystem, Evanston, Illinois (n = 123); Camille Jasper and Clau- dius Isaacs, Georgetown University, Washington, DC (n = 315); Patricia A. Ganz and Joyce L. Seldon, University of California, Los Angeles (n = 79); Fergus Couch, Mayo Clinic College of Medicine, Rochester, Minnesota (n = 96); Marc van Beurden and Laura Van’t Veer, Netherlands Cancer Institute, Amsterdam, the Netherlands (n = 121); Rosalind Eelles, Elizabeth Bancroft, Elizabeth Page, Lucia D’Mello, Susan Shanley, Audrey Ardern-Jones, Elena Castro, Anita Mitra, Kelly Kohut, and Jennifer Wiggins (Carrier Clinic Collaborators), In- stitute of Cancer Research and Royal Marsden NHS Foundation Trust, London, England (n = 111); Gareth Evans and Andrew Shenton, St Mary’s Hospital, Manchester, England (n = 301); Gail Tomlinson, Uni- versity of Texas-Southwestern, Dallas (n = 38); Shelly Cummings and Olufumilayo Olopade, University of Chicago, Chicago, Illinois (n = 53); Susan Domchek, Tara M. Friedman, Timothy Rebbeck, Jill Stoyer, Jacquelyn Powers, and Katherine Nathanson, University of Pennsylvania, Philadelphia (n = 296); Susan Neuhausen and Linda Steele, University of Utah, Salt Lake City, and University of California, San Diego (n = 230); Steven A. Narod, Women’s College Hospital, Toronto, Ontario, Canada (n = 54); and Ellen T. Matloff and Karina L. Brierly, Yale University, New Haven, Connecticut (n = 127).

Disclaimer: Dr Olopade, a member of JAMA’s Jour- nal Oversight Committee, did not have any input in the decision to accept the manuscript for publication.

Online-Only Material: eTable 1 and eTable 2 are available at http://www.jama.com.

Additional Contributions: This article is dedicated to the late Andrew Shenton, who contributed signifi- cantly to this research.

REFERENCES


