A Population-Based Study of Bilateral Prophylactic Mastectomy Efficacy in Women at Elevated Risk for Breast Cancer in Community Practices

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**Background:** Findings from several studies suggest that bilateral prophylactic mastectomy reduces breast cancer incidence by 90% or more, but the studies used highly selected patients from referral centers, and the comparison groups were not population based. We studied the efficacy of bilateral prophylactic mastectomy in women with elevated breast cancer risk cared for in community practices.

**Methods:** We conducted a retrospective case-cohort study of women aged 18 to 80 years with 1 or more breast cancer risk factors (family history of breast cancer, history of atypical hyperplasia, or ≥1 breast biopsies with benign findings). Using computerized data and medical records, we identified 276 women with bilateral prophylactic mastectomy and a stratified random sample of 196 women representing an underlying cohort of 666,800 women with elevated breast cancer risk without prophylactic mastectomy, and then we determined who developed breast cancer.

**Results:** Breast cancer developed in 1 woman (0.4%) after bilateral prophylactic mastectomy vs 26,800 women (4.0%) without prophylactic mastectomy. Stratifying by birth year, the hazard ratio for breast cancer occurrence after bilateral prophylactic mastectomy was 0.005 (95% confidence interval, 0.001-0.044). No woman with bilateral prophylactic mastectomy died of breast cancer vs a calculated 0.2% of women without prophylactic mastectomy.

**Conclusions:** Bilateral prophylactic mastectomy reduced breast cancer incidence in women at elevated risk for breast cancer cared for in community-based practices. However, the absolute risk of breast cancer incidence and death in women who did not undergo the procedure in these settings was relatively low.

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**STUDIES FROM REFERRAL CENTERS REPORT A SUBSTANTIAL REDUCTION IN BREAST CANCER INCIDENCE AFTER BILATERAL PROPHYLACTIC MASTECTOMY.**

Hartmann et al described a reduction of at least 90% in high- and moderate-risk women. The same investigators, along with Meijers-Heijboer et al and Rebbeck et al, demonstrated similar protection for women testing positive for deleterious BRCA1 and BRCA2 mutations.

We sought to determine whether bilateral prophylactic mastectomy is similarly efficacious among women with elevated breast cancer risk treated in community practices, where women who are offered the procedure are not as highly selected as in referral centers. In addition, unlike previous studies, this study is population based and includes women with elevated breast cancer risk not undergoing prophylactic mastectomy cared for in the same community practices as the women undergoing prophylactic mastectomy.

**METHODS**

**DESIGN AND SETTING**

We conducted this study in 6 health plans of the National Cancer Institute–funded Cancer Research Network: Group Health Cooperative, Washington; Harvard Pilgrim Health Care, Massachusetts; HealthPartners, Minnesota; and Kaiser Permanente Northwest (Oregon) and Northern and Southern California. Each site received institutional review board approval in accordance with assurances filed with and approved by the Department of Health and Human Services.

In this retrospective case-cohort study, patients were sampled based on exposure to bilateral prophylactic mastectomy and were followed for the outcome of breast cancer. In this design, statistical efficiency and a reduced data collection burden were achieved by oversampling unexposed women who experienced the outcome. Oversampling combined with the use of weights in the analysis allowed the data collected for the sample to represent the full cohort.
PATIENTS

Eligible patients included female enrollees aged 18 to 80 years between January 1, 1979, and December 31, 1998 (only 1981-1998 at 1 plan), who had at least 1 qualifying breast cancer risk factor. The most common qualifying risk factors were a family history of breast cancer, a personal history of atypical hyperplasia, and 1 or more breast biopsies with benign findings. A few women were eligible because of other qualifying risk factors (lobular carcinoma in situ, microcalcifications, or ovarian cancer). We excluded women with a personal history of breast cancer.

Among eligible patients, we included all women with bilateral prophylactic mastectomy (exposed women). However, rather than collect data for all 666,800 unexposed women without bilateral prophylactic mastectomy, the case-cohort design permitted oversampling of unexposed women who developed breast cancer. Results from the sampled women were used to represent all unexposed women by adding weights that accounted for sampling in the analysis.

Exposed women underwent a bilateral subcutaneous or more extensive mastectomy in the presence of elevated breast cancer risk and in the absence of a breast cancer diagnosis. All women with eligible procedures were identified from hospitalization data. Cancer registry data (4 sites) and ambulatory care data (2 sites) were used to exclude women with a personal history of breast cancer.

Unexposed women had elevated breast cancer risk without bilateral prophylactic mastectomy and were identified from membership data. We used cancer registry data (4 sites) and ambulatory care data (2 sites) to exclude women with a personal history of breast cancer and to identify women who developed breast cancer during the study. A stratified random subsample of unexposed women was selected to reflect the age and geographic distribution of the cohort. In each age and site stratum, unexposed women who developed breast cancer during the study were oversampled to ensure that the analysis would include an adequate number of women with the outcome. Stratified random sampling was performed using a priori sampling fractions. For example, the sample included 51, or 1.0%, of the 5,120 unexposed women born after 1945 who developed breast cancer during the study. This sampling strategy avoided the expense of collecting data for more than a half million unexposed women by allowing data for a sample to represent the entire group. We then used weights to account for sampling in the analysis.

DATA ELEMENTS

Medical records were reviewed to confirm eligibility, including bilateral prophylactic mastectomy and breast cancer risk factors. In addition we gathered information on breast procedures, breast cancer occurrence, and cause of death. Death information was supplemented with computerized state mortality data. Medical record abstractors were trained using a manual and a videotape, followed by an ongoing quality control program that included regular conference calls with the principal investigator (L.J.H.) and periodic re-abstraction of medical records to ensure accuracy and consistency. All data were gathered at the end of study follow-up.

STATISTICAL ANALYSIS

Women entered the cohort on the latest of the following dates: study start date (January 1, 1979, or, at 1 site, January 1, 1981), health plan enrollment, age 18 years, or first medical record notation of a breast cancer risk factor, the best available marker for when a woman and her physician would consider bilateral prophylactic mastectomy. Women exited the cohort at the time of failure (incident breast cancer) or when censoring occurred, on the earliest of the following dates: health plan disenrollment, age 80 years, death, or the study stop date (December 31, 1999). Twelve breast cancer diagnoses within 60 days of prophylactic mastectomy were considered to be incidental to the procedure and were not included as failures, although these women were followed for the development of incident breast cancer. A comparison analysis included incidental cancers as failures.

Results were adjusted for sampling. The adjustment weighted the contribution of each stratum by the sampling probability so that the combined results describe the full cohort. For example, the probability of being sampled was 1% for women born after 1945 who had breast cancer, so the results for these women were weighted by a factor of 100 in the analysis. The sampling probabilities and weights varied by the size of each stratum.

Cox proportional hazards regression with bilateral prophylactic mastectomy as a time-dependent covariate was used to evaluate the efficacy of bilateral prophylactic mastectomy in preventing breast cancer. Calendar time was used as the time axis, and the analysis was stratified by health plan and birth year (before 1945 vs 1945 or later). Because only 1 woman developed breast cancer after prophylactic mastectomy, we could not adjust for other potential confounders owing to model instability when additional factors were included. To obtain an unbiased estimate of the hazard ratio with appropriate standard errors, we accounted for sampling by using a variant of the method developed for a standard case-cohort analysis with a robust covariance matrix.5,6 The analysis was conducted using the PHREG procedure (version 8.2; SAS Institute Inc, Cary, NC), with an offset to accommodate the sampling techniques and an empirical sandwich estimator of the covariance matrix.

We used the model of Gail et al7 as a second method to determine the efficacy of bilateral prophylactic mastectomy. The model assesses risk using family history of breast cancer, previous breast biopsy, previous diagnosis of atypical hyperplasia, age at menarche, age at first birth, and current age. For each exposed woman undergoing prophylactic mastectomy, we used the model to estimate the probability of developing breast cancer in the subsequent 10 years if the women had not undergone the procedure and to estimate the number of breast cancers that might have occurred in the absence of prophylactic mastectomy. Ten years was used because this matched the actual follow-up time in the study, thus permitting a direct comparison between observed and expected incident breast cancers. Estimated breast cancer risk was not calculated for unexposed women because actual risk was available in the study data and was incorporated into the proportional hazards analysis.

RESULTS

Using computerized data, we identified 279 exposed women who underwent bilateral prophylactic mastectomy, with 276 women eligible after medical record review; 4 of the ineligible women had undergone prophylactic mastectomy outside the study period, and 17 had no breast cancer risk factor noted. Of 689 unexposed women without bilateral prophylactic mastectomy initially selected for possible inclusion in the comparison cohort, 196 were eligible and represented an underlying cohort of 666,800 women with elevated breast cancer risk without prophylactic mastectomy. Unexposed women were excluded for having no breast cancer risk factor in the medical record (n=401), incomplete medical records (n=89), and a personal history of breast cancer or other qualifying risk factors (n=89).
prophylactic mastectomy (n=3). The large number of medical records reviewed relative to the number of eligible patients was because of the inability to identify women as being at risk for breast cancer before medical record review.

The most common breast cancer risk factor was family history (Table 1). Women with bilateral prophylactic mastectomy had a slightly higher prevalence of first-degree relatives with breast cancer than did unexposed women (62% vs 57%). Among women without a family history of breast cancer, atypical hyperplasia was more common in women with prophylactic mastectomy than in those without. More women with vs without prophylactic mastectomy had multiple risk factors (65% vs 12%).

The mean age at bilateral prophylactic mastectomy was 45 years (range, 23-74 years). Compared with unexposed women with elevated breast cancer risk, women with prophylactic mastectomy were of similar age at notification of first breast cancer risk factor but were more likely to be white (Table 2). The mean follow-up was 10.3 years for women with bilateral prophylactic mastectomy and 6.2 years for unexposed women.

Breast cancer developed in 1 (0.4%) of 276 women after bilateral prophylactic mastectomy vs a calculated 26800 (4.0%) of 666800 unexposed women with elevated breast cancer risk. Taking into account the sampling scheme and stratifying by birth year and health plan, the hazard ratio for breast cancer occurrence after bilateral prophylactic mastectomy was 0.005 (95% confidence interval, 0.001-0.044).

By using the model of Gail et al7 to compare expected and observed incident breast cancers, we confirmed the results of the case-cohort analysis (Table 3). Whereas the model suggested that 15 breast cancers would have occurred in the absence of bilateral prophylactic mastectomy, none occurred. The 1 case of breast cancer after prophylactic mastectomy occurred in 1 of the 62 women for whom the model of Gail et al could not be used because her age was below those covered by the model.

The woman who developed breast cancer after bilateral prophylactic mastectomy underwent the procedure at age 27 years. She was diagnosed as having node-negative, regionally staged breast cancer 15 months after prophylactic mastectomy. She had 4 relatives with breast cancer, including 2 first-degree relatives, 1 second-degree relative, and 1 third-degree relative.

### Table 1. Breast Cancer Risk Factors in Women With and Without Bilateral Prophylactic Mastectomy in Community Practices, 1979-1998*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Bilateral Prophylactic Mastectomy (n = 276)</th>
<th>No Bilateral Prophylactic Mastectomy (n = 666800)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of breast cancer,</td>
<td>24 3</td>
<td>25 24</td>
</tr>
<tr>
<td>with or without other risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 First-degree relatives affected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 First-degree relative with other affected relatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 First-degree relative without other affected relatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 Second-degree relatives affected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Second-degree relative affected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any third-degree or more distant relatives affected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of atypical hyperplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of breast biopsy, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4 2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5 3</td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td>3 0</td>
<td></td>
</tr>
<tr>
<td>Other (lobular carcinoma in situ, microcalcifications, or a history of ovarian cancer)</td>
<td>0 2</td>
<td></td>
</tr>
<tr>
<td>Breast cancer risk factors noted, total No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>35 88</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>33 4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>24 8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>8 0</td>
<td></td>
</tr>
</tbody>
</table>

*Except for the total number of risk factors, the categories are mutually exclusive and hierarchical in the order shown. For example, a woman meeting any of the family history criteria is eligible for that reason and would not be counted later if she has an additional reason for eligibility.

†Comparison cohort results are based on data from 196 sampled women with elevated breast cancer risk without bilateral prophylactic mastectomy, with results weighted to account for sampling.
breast cancer (mother, maternal grandmother, paternal aunt, and female paternal cousin), with no other breast cancer risk factors noted. Of the unexposed women with elevated breast cancer risk who developed breast cancer, 22% had a first-degree relative with breast cancer. The cancers for 24% were node positive and were staged as in situ in 15%, local in 56%, and regional in 29%. Whereas the woman with breast cancer after prophylactic mastectomy remained alive at the end of the study, 1600 unexposed women with elevated breast cancer risk (0.2%) had died of breast cancer.

At surgery, 12 women were found to have incidental (previously undetected) breast cancer. Their mean age was 49.0 years (range, 30-74 years); 5 incidental tumors were in situ, 4 were local, 2 were regional, and 1 was not staged. For the 7 tumors with size noted, the mean size was 9.7 mm (range, 1-15 mm). Of 3 women with lymph nodes available for examination, 2 had positive nodes. No second breast cancers or breast cancer deaths occurred in these women. When incidental cancers were analyzed as failures, the hazard ratio for breast cancer occurrence after bilateral prophylactic mastectomy was 0.088 (95% confidence interval, 0.031-0.248).

**COMMENT**

We found that bilateral prophylactic mastectomy reduced by approximately 95% or more the occurrence of breast cancer among women with elevated breast cancer risk cared for in community practices. With only 1 outcome in women with prophylactic mastectomy, it is difficult to precisely estimate the hazard ratio and its confidence interval. However, estimates from the model of Gail et al7 also suggest a strong protective effect, with prophylactic mastectomy estimated to have prevented 15 breast cancers among women who were 35 years or older at the time of their procedure. Finally, even when we considered as failures incidental breast cancers found at the time of prophylactic mastectomy, we found a marked reduction in subsequent breast cancer occurrence, with the lower confidence interval at 75%. Our results, therefore, suggest a clinically meaningful reduction in breast cancer risk after bilateral prophylactic mastectomy.

However, the absolute underlying risk of breast cancer and death from breast cancer was low. Only 4% of the unexposed women with elevated breast cancer risk developed breast cancer during mean follow-up of 6 years. No woman with bilateral prophylactic mastectomy died of breast cancer vs 0.2% of the unexposed women. Because there was only 1 breast cancer occurrence after prophylactic mastectomy, we could not identify subgroups in which the procedure would be more or less efficacious, including whether subcutaneous and total mastectomy offer equivalent protection.

Women with elevated breast cancer risk have several risk reduction options other than bilateral prophylactic mastectomy. Prophylactic oophorectomy reduces breast cancer risk by approximately 30% to 50%.9,10 Close surveillance with clinical breast examination and mammography permits early detection and treatment, but the overall efficacy for women with elevated breast cancer risk is not known.10 Tamoxifen therapy reduces breast cancer occurrence by 49% in women at elevated risk.11,12 Decisions about risk reduction are complex and highly individualized given the unique benefits and risks of each approach.

Most women undergoing bilateral prophylactic mastectomy in our study seem to be similar to the women classified as having moderate risk by Hartmann and colleagues.1 Genetic testing was not available or was not performed on women in this study, but the family histories of most patients (38% had no first-degree relatives with breast cancer and another 13% had only 1 first-degree relative with breast cancer) make it unlikely that they had a deleterious BRCA1 or BRCA2 mutation. Increasingly, prophylactic mastectomy will be offered primarily to women with positive test results for genetic mutations. However, some women may not have access to testing, may choose not to be tested, may have negative test results yet remain concerned about their elevated breast cancer risk, or may be at only moderately elevated breast cancer risk but prefer the benefits and risks of a surgical intervention to the risks and benefits of chemoprevention or close surveillance. Our results provide evidence that these women will experience a clinically meaningful reduction in breast cancer risk after bilateral prophylactic mastectomy.

Several strengths and limitations of this study merit consideration. Data were collected retrospectively, but the cohort design is inherently prospective in that the analysis patients are followed from exposure (bilateral prophylactic mastectomy) until they are censored or fail (develop incident breast cancer). According to their medical records, breast cancer risk in unexposed women was not as high as that in women who underwent prophylactic mastectomy. Higher-risk women may be more likely to undergo the procedure, or medical record notation of risk may be more complete. Reduced risk in unexposed women would result in an underestimate of prophylactic mastectomy efficacy. The model of Gail et al7 does not incorporate second-degree family history of breast cancer or personal history of lobular neoplasia13,14 and thus may underestimate breast cancer risk. Owing to the large number of women cared for in these community practices, our study, with a population-based control group, avoids biases that might arise when studies include biologically related women or women who have also un-

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<table>
<thead>
<tr>
<th>Age, y</th>
<th>Estimate* of 10-y Breast Cancer Risk, mean, % (n = 214)†</th>
<th>Expected Breast Cancers, No. (n = 214)†</th>
<th>Observed Breast Cancers, No. (n = 214)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-39</td>
<td>4.1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>40-49</td>
<td>5.0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>50-59</td>
<td>7.2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>60-74</td>
<td>9.7</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

* Determined according to the model of Gail et al.7
† Excludes 62 women with prophylactic mastectomy younger than 35 years or with a history of lobular carcinoma in situ at the time of bilateral prophylactic mastectomy; includes 1 woman who developed breast cancer after prophylactic mastectomy.
derned prophylactic oophorectomy, which was rare in our study. The appropriate handling of cancers discovered incidental to bilateral prophylactic mastectomy is subject to debate. Removal of incidental cancers from the analysis may underestimate the presence of breast cancer in the cohort and may overstate the protective effect of prophylactic mastectomy. Yet, these previously undiscovered cancers represent a success of prophylactic mastectomy and thus should not be considered failures. A review of 7 autopsy studies of women not known to have breast cancer while alive found that the median prevalence of invasive breast cancer was 1.3% (range, 0%-1.8%) and of ductal carcinoma in situ was 8.9% (range, 0%-14.7%). The frequency of incidental breast cancer in our study is in line with these results. The protective effect of bilateral prophylactic mastectomy is stronger when incidental cancers are not counted as failures, but the protective effect remains strong when they are counted.

Most women at elevated risk for breast cancer are cared for in community practices rather than referral centers. Our results extend the findings of Hartmann, and Rebbeck and their colleagues, who found that bilateral prophylactic mastectomy substantially reduces the incidence of breast cancer in women with deleterious genetic mutations and others with elevated breast cancer risk referred to specialized treatment centers. These results probably were achieved by a limited number of surgeons performing prophylactic mastectomy more frequently than might be true in community practices. Our similar results from 6 health plans in different geographic areas suggest that the benefit extends beyond women at very elevated risk cared for at referral centers and may generalize beyond specialized surgeons.

The present study did not address the appropriateness of bilateral prophylactic mastectomy for women who have a moderately elevated risk of breast cancer. Although the procedure seems to reduce the risk of breast cancer more than any other management option, we found that the underlying absolute risk of breast cancer in most women who underwent prophylactic mastectomy in our study was modest and that the risk of dying of breast cancer was small. Women and physicians should consider the risk of breast cancer before choosing preventive options.

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REFERENCES