Recognizing a Primary Research Article

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Recognizing a Primary Research Article

Most research articles have the following sections:

• Abstract
• Introduction/Background
• Purpose of study
• Review of the Literature
• Methods
• Data Analysis
• Discussion of the Results
• Limits of the Study
• Suggestions for further research
• Conclusion
• References
Detailed Abstract

**ABSTRACT**

**Background**

Women with a BRCA1 or BRCA2 mutation have a high risk of breast cancer and may choose to undergo prophylactic bilateral mastectomy. We investigated the efficacy of this procedure in such women.

**Methods**

We conducted a prospective study of 139 women with a pathogenic BRCA1 or BRCA2 mutation who were enrolled in a breast cancer surveillance program at the Rotterdam Family Cancer Clinic. At the time of enrollment, none of the women had a history of breast cancer. Seventy-six of these women eventually underwent prophylactic mastectomy, and the other 63 remained under regular surveillance. The effect of mastectomy on the incidence of breast cancer was analyzed by the Cox proportional hazards method in which mastectomy was modeled as an time-dependent covariate.

**Results**

No cases of breast cancer were observed after prophylactic mastectomy after a mean of 5.3 years follow-up of 2.9 ± 1.4 years, whereas eight breast cancers developed in women under regular surveillance after a median follow-up of 3.9 ± 1.5 years (P = 0.003; hazard ratio, 0.35; 95% confidence interval, 0.18 to 0.69). The adjusted mean five-year incidence of breast cancer among all women in the surveillance group was 17.17%. On the basis of an exponential model, the yearly incidence of breast cancer in this group was 2.8%. The observed number of breast cancers in the surveillance group was consistent with the expected number ratio of observed to expected cases, 1.07; 95% confidence interval, 0.64 to 1.77; P = 0.80). The identification of the breast-cancer-susceptibility genes BRCA1 and BRCA2 evoked widespread interest in genetic testing among women at risk for a mutation in these genes. We found that 87 women were at risk for breast cancer who had a 50% chance of carrying a BRCA2 or BRCA2 mutation through genetic testing. This result indicates that the need to determine the efficacy of the various options for reducing the risk of breast cancer and for early detection in women with a BRCA1 or BRCA2 mutation.

**Conclusions**

Women with a BRCA1 or BRCA2 mutation have a cumulative lifetime risk of breast cancer (up to the age of 70 years) of 35 to 85% and of invasive breast cancer of 13 to 60%.

In these women the risk of breast cancer begins to increase near the age of 25 years, and their overall survival once breast cancer develops is similar to that of age-matched women with sporadic cases of breast cancer, both the 10-year survival rate is about 50%.

Current risk-reduction strategies for women with a BRCA1 or BRCA2 mutation include regular surveillance, prophylactic mastectomy, tamoxifen, or both and chemoprevention. In our experience, 50 percent of women who have a BRCA1 or BRCA2 mutation have chosen to undergo prophylactic bilateral mastectomy.

**Introduction, Background, Review of the Literature**

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Current risk-reduction strategies for women with a BRCA1 or BRCA2 mutation include regular surveillance, prophylactic mastectomy, tamoxifen, or both and chemoprevention. In our experience, 50 percent of women who have a BRCA1 or BRCA2 mutation have chosen to undergo prophylactic bilateral mastectomy. Until now, however, there have been only retrospective studies of the efficacy of the procedure in women with an increased risk of breast can-
Purpose of the Study

We investigated the efficacy of prophylactic mastectomy in women with a proven pathogenic BRCA1 or BRCA2 mutation because a randomized trial is impossible for ethical reasons, and performed a prospective cohort study of women in a single institution who chose either prophylactic mastectomy or regular surveillance.

METHODS

Study Subjects

Beginning on January 1, 1992, we studied all women with a BRCA1 or BRCA2 mutation who were being monitored for breast cancer because of familial history of breast cancer, ovarian cancer, or both at the Hamden Breast Cancer Group in Hamden, Connecticut. We included all women who had been given a positive test date before January 1, 2000. Women with a BRCA1 or BRCA2 mutation in whom breast cancer developed before January 1, 1992, and one woman in whom breast cancer was detected as in the screening was excluded. By the date January 1, 1992, was shown because of the inadequacy of our family history to make clinical risk, we excluded 100 women familiar with breast cancer. Finally, 76 of these women chose to undergo prophylactic bilateral mastectomy before the end of the follow-up period (March 1, 2001), whereas the other 68 women chose to remain under regular surveillance. In all two women prophylactic mastectomy was performed after the molecular diagnosis was established.

Data Collection and Follow-up

Information on diagnoses and the occurrence of cancer was extracted from the women's medical files. All women were regularly monitored at our clinic until March 1, 2001, and were enroled in clinical research programs approved by our medical ethics committee (protocol D101K14-17, published in 1999). We obtained a detailed report of all mammography tests and of all breast biopsies performed by breast surgeons. A breast cancer was considered to be of the same histological type as that of the patient and was confirmed by review of all medical records. Prophylactic mastectomy was defined as bilateral mastectomy before the age of 56 years and was performed prophylactically in the case of 76 women, for benign disease in the case of 7 women, for ovarian cancer in the case of 7 women, and for breast cancer in the case of 1 woman (Table 1). No woman was lost to follow-up after prophylactic mastectomy. Of the women in the surveillance group, three died of ovarian cancer and one was close to be monitored in another hospital for practical reasons.

Surgical Techniques and Surveillance

In all, men were treated with the same surgical approach, as the Family Breast Cancer Group. In 76 of 76 women, the breast were removed with saline implants by a plastic surgeon in the same woman, followed later by a single reconstruction. According to current guidelines, regular surveillance for breast cancer detection is monthly breast self-examination, a clinical breast examination every six months, and yearly mammography. Since 1999, magnetic resonance imaging (MRI) has been an option at our clinic for women with mammographically dense tissue and surgery within the following were performed no more than three months before surgery: a physical examination of the breast, mammography, or MRI. After prophylactic mastectomy, the chest wall and lymph node biopsy were performed every six months. In women, mammography of the chest was performed once a year after prophylactic mastectomy.

Analysis of BRCA1 and BRCA2 Mutations and Histologic Examination

DNA analysis was performed according to standard procedures on all BRCA1 and BRCA2 mutations. We used DNA from peripheral blood leukocytes. All BRCA1 and BRCA2 mutations were pathogenic since they led to a premature truncation of the BRCA1 or BRCA2 protein.

Main outcome measures were death from breast cancer, death from other causes, and death from other causes after death from breast cancer. The age at entry in the surveillance group was based on the date of entry on which surveillance was initiated.

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Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 11.5, SPSS, Chicago, Illinois) and R (version 2.5.1, statsoft, Tulsa, Oklahoma). The significance level was 5% (p < 0.05). All tests were two-sided.
### Table 2. Characteristics of the Eight Women in the Surveillance Group in Whom Breast Cancer Developed

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Diagnosis</th>
<th>Menopausal Status</th>
<th>Familial History</th>
<th>Initial Genetic Testing Result</th>
<th>Current Status</th>
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<tr>
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</tr>
<tr>
<td>2</td>
<td>58</td>
<td>No</td>
<td>No</td>
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<td>Died of breast cancer</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
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<tr>
<td>7</td>
<td>56</td>
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<td>No</td>
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<td>NED</td>
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<tr>
<td>8</td>
<td>57</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>NED</td>
</tr>
</tbody>
</table>

*NED denotes no evidence of disease.

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### Table 3. Characteristics of the Twelve Women in the Surveillance Group in Whom Breast Cancer Developed

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Diagnosis</th>
<th>Menopausal Status</th>
<th>Familial History</th>
<th>Initial Genetic Testing Result</th>
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<td>C/7; wild type</td>
<td>3/53</td>
<td>SC/SC</td>
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<td>D/15</td>
<td>3/53</td>
<td>SC/SC</td>
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<tr>
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<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>D/15</td>
<td>3/53</td>
<td>SC/SC</td>
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<td>7</td>
<td>10</td>
<td>C/7; wild type</td>
<td>3/53</td>
<td>SC/SC</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>D/15</td>
<td>3/53</td>
<td>SC/SC</td>
<td>SC</td>
</tr>
</tbody>
</table>

*SC denotes bilateral mammography, CBIR: digital breast imaging, MRI: magnetic resonance imaging, HR: high probability of hormone exposure, NA: not done, and SM: mammography.
Results

Characteristics of the Women

Table 1 lists the general characteristics of the women who chose to undergo prophylactic mastectomy and those who opted for surveillance. Significantly more women in the mastectomy group in the surveillance group had undergone a premenopausal oophorectomy (44 vs. 24 [58 percent vs. 38 percent], P = 0.08). All gynecologic cancers occurred before the age of 56 years; the two such cases in the mastectomy group were ovarian cancer, stage IIC. There were no significant differences between the two groups with respect to age, average duration of follow-up after entry into the study, follow-up after preoperative surveillance, and type of mutation. The 26 distinct mutations — 23 in BRCA1 and 3 in BRCA2 — were distributed in a similar fashion in the two groups. The 189 women were from a pool of 70 families; the number of women from each family ranged from 1 to 5.

The mean (± SE) duration of follow-up was 2.8±1.4 years (219 woman-years) in the mastectomy group and 3.0±1.6 years (190 woman-years) in the surveillance group (Table 1). The total number of woman-years of surveillance increased from 190 to 316 when the 128 woman-years of surveillance before prophylactic mastectomy were added.

Incidence of Breast Cancer

After prophylactic mastectomy no case of invasive breast cancer was observed in any of the 76 women during 219 woman-years at risk (Fig. 1). In the surveillance group eight invasive breast cancers were detected during 318 woman-years at risk, for a yearly incidence of 2.5 percent. The ratio of observed cases to expected cases was 1.2 (95 percent confidence interval,
Discussion of the Results

0.4 to 3.7; P = 0.80). All the affected women were from different families. The actuarial mean five-year incidence of breast cancer in the women in the surveillance group (Fig. 1) was 17.7 percent, but the number of women at risk at five years was only eight. To obtain a more stable estimate with longer periods of follow-up, we calculated cumulative incidence probabilities with the use of an exponential model in which the hazard rate was assumed to be constant. According to this model, the yearly incidence of breast cancer was 2.8 percent and the five-year cumulative incidence was 12 percent (95 percent confidence interval, 6 to 23 percent) (Fig. 1). Disregarding the years of surveillance before prophylactic mastectomy and thus restricting the actuarial analysis to the 63 women in the surveillance group, we estimated that the five-year risk of breast cancer was 24.9 percent.

Con parallel-hazard analysis showed that mastectomy significantly (P = 0.008) decreased the incidence of breast cancer (hazard ratio, 0.95; 95 percent confidence interval, 0.44 to 2.16). After adjustment for the effects of mastectomy, the protective effects of mammography remained statistically significant (P = 0.01).

Outcome in the Women with Breast Cancer

None of the eight patients in the surveillance group in whom breast cancer developed had been scheduled to undergo prophylactic mastectomy at the time of the diagnosis. The characteristics of the women and the tumors are described in Tables 2 and 3, respectively. Patients 7 and 8 underwent bilateral prophylactic mastectomy 14 and 12 months, respectively, before the diagnosis of breast cancer. Of the eight cancers, four (in Patients 1, 2, 4, and 6) were detected between screening sessions (so-called interval cancers). In these four patients the interval from screening to diagnosis was two to five months. The cancers in the other four patients (Patients 3, 5, 7, and 8) were detected during a screening session. Patient 1 became symptomatic eight weeks after her first clinical breast-cancer screening, the results of which were negative. In four of the eight patients, breast cancer was detected before the molecular diagnosis was made.

Histologic Findings in the Malignant Group

Invasive cancer was not detected in any of the specimens obtained at the time of prophylactic mastectomy. One 44-year-old woman with a BRCA1 mutation had lobular carcinoma in situ.

**DISCUSSION**

In this prospective study we assessed the incidence of breast cancer in 139 women with a BRCA1 or BRCA2 mutation who chose to undergo either prophylactic mastectomy or regular surveillance. Whereas breast cancer developed in 8 of 63 women in the surveillance group, no cases of breast cancer occurred among the 76 women who underwent prophylactic mastectomy. The observed number of breast cancers in the group under surveillance is compatible with the reported incidence of breast cancer in women with a BRCA1 or BRCA2 mutation. As compared with the incidence in the surveillance group, the incidence of breast cancer in the prophylactic-mastectomy group was significantly reduced (P = 0.0003), but the mean follow-up of three years calls for a cautious interpretation of our results.

**TABLE 2. CHARACTERISTICS OF THE EIGHT WOMEN IN THE SURVEILLANCE GROUP IN WHOM BREAST CANCER DEVELOPED.**

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>AGE AT DIAGNOSIS</th>
<th>HORMONE TREATMENT</th>
<th>PROPHYLACTIC MASTECTOMY</th>
<th>PROPHYLACTIC OVARIAN MAJESTER</th>
<th>CHEST WALL TREATMENT</th>
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Conclusion

Limits of the Study & Further Research

References

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