Recognizing a Primary or Empirical Research Article

Elizabeth Bucciarelli
Health Sciences Librarian
ebucciare@emich.edu
734.487.2506
Recognizing a Primary or Empirical Research Article

Most primary or empirical research articles have the following sections, however, these exact terms may not be used:

- 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
Recognizing a Primary or Empirical Research Article

- These two terms, primary and empirical, are used interchangeably

- This type of article reports the results of a study that uses data derived from actual observation or experimentation
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 37% of women without breast cancer who had a 50% chance of carrying a BRCA1 or BRCA2 mutation requested genetic testing. This result indicates 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.

Women with a BRCA1 or BRCA2 mutation have a cumulative lifetime risk of male breast cancer (up to the age of 70 years) of 55 to 88 percent and of invasive epithelial ovarian cancer of 13 to 60 percent. 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 patients with sporadic cases of breast cancer; both the 10-year survival rate is about 50 percent.

Current risk-reduction strategies for women with a BRCA1 or BRCA2 mutation include regular surveillance (prophylactic mastectomy, oophorectomy, or both) and chemoprevention. In our experience, 70 percent of women who have a BRCA1 or BRCA2 mutation have chosen to undergo prophylactic bilateral mastectomy.
Methods

Purpose of the Study

Beginning on January 1, 1992, we studied all women with a BRCA1 or BRCA2 mutation who were being monitored for breast cancer because of prior diagnosis of breast cancer or ovarian cancer, or both, at the Dana-Farber Cancer Institute in Boston, the Netherlands, and the United States. Women who had been given a positive diagnostic marker before January 1, 1992 were not included. By late 2000, 2,108 women had been studied. All women who were being monitored had been identified through clinical screening programs provided by our medical centers. All women were enrolled in our clinical trial program approved by our medical ethics committee, and all gave written informed consent.

We found that the incidence of breast cancer in women with a BRCA1 or BRCA2 mutation was higher than in the general population. The incidence of breast cancer in the general population is lower than in the population of women with a BRCA1 or BRCA2 mutation.

We identified several risk factors for breast cancer in women with a BRCA1 or BRCA2 mutation, including:

- Age at diagnosis
- Number of first-degree relatives with breast cancer
- Age at onset of breast cancer
- Menopause status
- Family history

We used these risk factors to create a risk assessment tool for women with a BRCA1 or BRCA2 mutation.

Analysis of BRCA1 and BRCA2 Mutations and Histologic Examinations

DNA analysis was performed according to standard procedures. DNA from blood samples was used in all women. DNA was extracted from blood samples and the PCR products were sequenced. The sequencing results were analyzed and compared to the wild-type sequence.

Statistical Analysis

Statistical analysis was performed using the Chi-square test and the Fisher's exact test. The significance level was set at p < 0.05.
### Table 2: Characteristics of the Eight Women in the Surveillance Group in Whom Breast Cancer Occurred

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Diagnosis</th>
<th>Menopause</th>
<th>Prior Oophorectomy</th>
<th>Prior Chemotherapy</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NED</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Died of breast cancer</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NED</td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NED</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NED</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NED</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>NED</td>
</tr>
<tr>
<td>8</td>
<td>62</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>NED</td>
</tr>
</tbody>
</table>

*Note: NED denotes no evidence of disease.

### Table 3: Characteristics of the Women in the Four Women in the Surveillance Group in Whom Breast Cancer was Diagnosed

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time at Diagnosis</th>
<th>No. of Oophorectomy/Total No. of Women</th>
<th>Menopause</th>
<th>ER Status</th>
<th>PR Status</th>
<th>Age at Diagnosis</th>
<th>Prior Chemotherapy</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>1/10</td>
<td>No</td>
<td>ER 1</td>
<td>PR 1</td>
<td>25</td>
<td>No</td>
<td>NED</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>2/10</td>
<td>No</td>
<td>ER 1</td>
<td>PR 1</td>
<td>32</td>
<td>Yes</td>
<td>NED</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>3/10</td>
<td>No</td>
<td>ER 1</td>
<td>PR 1</td>
<td>45</td>
<td>No</td>
<td>NED</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>4/10</td>
<td>No</td>
<td>ER 1</td>
<td>PR 1</td>
<td>58</td>
<td>Yes</td>
<td>NED</td>
</tr>
</tbody>
</table>

*Note: NED denotes no evidence of disease.
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 than in the surveillance group had undergone a premenopausal oophorectomy (44 vs. 24 [58 percent vs. 38 percent], P = 0.03). All gynecologic cancers occurred before the age of 56 years; the two such cases in the mastectomy group were ovarian cancer, stage IC. 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 prophylactic oophorectomy, and type of mutation. The 28 distinct mutations — 23 in BRCA1 and 5 in BRCA2 — were distributed in a similar fashion in the two groups. The 189 women were from a pool of 78 families, the number of women from each family ranged from 1 to 5.

The mean (±SE) duration of follow-up was 2.9±1.4 years (219 woman-years) in the mastectomy group and 3.0±1.8 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 survival before prophylactic mastectomy was 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 accrual mean five-year incidence of breast cancer in the women in the surveillance group (Fig. 1) was 17.2 percent, but the number of women at risk for 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 2.5 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 accrual analysis to the 63 women in the surveillance group, we estimated that the five-year risk of breast cancer was 24.9 percent.

Con-proportional-hazard analysis showed that mastectomy significantly (P = 0.008) decreased the incidence of breast cancer (hazard ratio, 0.95; 95 percent confidence interval, 0.80 to 1.36). After adjustment for the change in menstrual status, the protective effect of mastectomy 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 Mammary Gland

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 83 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 = 0.008), but the mean follow-up of three years calls for a cautious interpretation of our results.

<table>
<thead>
<tr>
<th>Table 2. Characteristics of the Eight Women in the Surveillance Group in Whom Breast Cancer Developed.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>
tomy, women with a **BRCA1** or **BRCA2** mutation may choose no undertakes bilateral oophorectomy before menopause, chemoprevention, or both to reduce the risk of breast cancer. Such interventions may reduce the risk of breast cancer by about 50%—60%, but the use of tamoxifen as a preventive agent has been questioned in view of its long-term side effects.  

Prophylactic mastectomy is a highly personal decision. In counseling high-risk women, the protective effect of prophylactic mastectomy must be weighed against possible surgical complications and psychological problems. Up to 30% of the women who undergo the procedure will have surgical complications, depending on the type of surgery and the length of follow-up. A long-term study of prophylactic mastectomy reported unanticipated repeated operations in 49 percent of women, but these results may not be applicable to prophylactic mastectomies as they are currently performed. Psychological studies of women who had undergone a prophylactic mastectomy did not find that, overall, the procedure had detrimental effects on body image and sexuality. In conclusions, our data and those of Harratt et al. indicate that prophylactic bilateral total mastectomy substantially reduced the incidence of breast cancer among women with a **BRCA1** or **BRCA2** mutation. Nevertheless, longer follow-up and studies of more patients are required to establish the protective effect and determine the long-term complications of this procedure.

We are indebted to Medtronic (Thermo-Lotus and Lin on Zen). For conducting surveillance for Early Stage Lung for breast reconstruction in the patients with St Jude and Leem Aboun for assistance with data analysis; to Ellen Cripps and Jane Collins for data collection; to Dr. Foley and Dr. Viozzi for medical assistance; and to Prince for assistance with the preparation of the manuscript.

**REFERENCES**


Ebuucciarelli 6/2019