Survival in Epithelial Ovarian Cancer Patients with Prior Breast Cancer

Valerie McGuire, Alice S. Whittemore, Robin Norris, and Ingrid Oakley-Girvan

Ovarian cancer patients who carry germ-line BRCA1 mutations may have improved survival compared with ovarian cancer patients without these mutations. To evaluate this hypothesis, the authors compared survival in ovarian cancer patients who had a history of prior breast cancer with that of patients without such a history. Specifically, they used data from the population-based US Surveillance, Epidemiology, and End Results (SEER) Program to assess time to death from ovarian cancer among ovarian cancer patients with and without a prior breast cancer. All 25,637 White women diagnosed with invasive epithelial ovarian cancer in SEER registries between 1973 and 1995 were included. Of these, 824 women had had a prior breast cancer diagnosis. The ovarian cancer death rate among women with prior breast cancer was significantly lower than that of women with ovarian cancer only, adjusted for age and stage at ovarian cancer diagnosis. The survival advantage was most pronounced among older women and among those whose ovarian cancers were more advanced at the time of diagnosis. These results lend indirect support to prior findings of improved ovarian cancer survival in BRCA1 mutation carriers. Am J Epidemiol 2000;152:528–32.

breast neoplasms; genes, BRCA1; ovarian neoplasms; survival

Epithelial ovarian cancer is the sixth most common cancer among women and is the leading cause of death from gynecologic malignancies (1). The overall 5-year survival rate for ovarian cancer in the United States is 46 percent (2). Over 65 percent of patients present with advanced disease, and their 5-year survival is 20 percent (2). Carriers of germ-line mutations of the gene BRCA1 have an increased risk of ovarian cancer. The risk by age 70 years among BRCA1 heterozygotes has been estimated as 16 percent (3), as 21 percent (4), and as 40 percent (5). These risks are considerably higher than the corresponding risk of 1 percent in the general population (4).

Several studies have investigated the relation between BRCA1 mutation status and survival from ovarian cancer, with conflicting results (6–11). Data from some of them suggest that ovarian cancer patients who carry germ-line BRCA1 mutations have improved survival compared with ovarian cancer patients without these mutations (6–8). To account for these observations, it has been speculated that the survival advantage for BRCA1 mutation carriers reflects better response to chemotherapy (8). However, other studies have reported similar survival of ovarian cancer patients with and without BRCA1 mutations (9–11). The majority of these studies used clinic-based samples of patients with and without mutations, who may have been selected for factors related to survival. To further evaluate the hypothesis of improved survival without such selection bias, we compared survival in a population-based sample of women who had a history of prior breast cancer with that of women without such a history. This comparison is relevant because it has been estimated that some 88 percent of women with both breast and ovarian cancer carry BRCA1 mutations (12), while less than 5 percent of all ovarian cancer patients do so (4, 13). (The 88 percent estimate was obtained from women attending high-risk clinics and, thus, may be somewhat higher than would be seen in a sample of such patients from the general population.)

MATERIALS AND METHODS

Study population

We analyzed data from nine population-based cancer registries operated by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. The registries are located in Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, northern California, Seattle, and Utah. All 25,637 White women who were diagnosed with invasive epithelial ovarian cancer between 1973 and 1995 were included. Of these, 824 women were reported in a SEER registry as having had a prior breast cancer diagnosis. We excluded women who were diagnosed with ovarian cancer of low malignant potential (n = 1,591). We also excluded non-White women with epithelial ovarian cancer (n = 2,822), because too few of these women had reported prior breast cancer diagnoses to permit separate analysis.
**Statistical analysis**

The event of interest was death from ovarian cancer as determined by information from death certificates. The SEER registries obtain cause of death information from the state Vital Statistics Departments, which determine whether the conditions listed on the death certificates are immediate or underlying causes of death. If a woman died from causes other than ovarian cancer, her time to death was treated as censored.

We computed Kaplan-Meier estimates of ovarian cancer survival probability versus time since ovarian cancer diagnosis (14). We used Poisson regression methods (15, 16) to calculate expected numbers of deaths among epithelial ovarian cancer patients with a prior history of breast cancer, based on rates in women without such a history, adjusted for age at diagnosis, stage of disease at diagnosis, and geographic location of the SEER registry. To test the null hypothesis that patients with and without breast cancer were similar with respect to various characteristics (age at diagnosis, stage of disease at diagnosis, histologic subtype of ovarian cancer), we used the standard chi-squared test for homogeneity in a $2 \times k$ table, where $k$ is the number of categories of a given characteristic (17).

We evaluated survival specific for age at ovarian cancer diagnosis (<35, 35–44, 45–54, 55–64, 65–74, 75–84, ≥85 years), stage of disease at ovarian cancer diagnosis (localized, regional, distant, unstaged), and SEER registry (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, northern California, Seattle, Utah). The SEER Program classifies an ovarian cancer as localized (cancer is confined to the ovary), regional (cancer extends beyond the ovary into surrounding organs and tissues or regional lymph nodes), or distant (cancer has spread to sites remote from the ovary). Other potential confounders, such as family history, parity, and oral contraceptive use, are not available in the SEER data.

**RESULTS**

Table 1 summarizes the clinical and pathologic features of the two groups of women. Women with a prior breast cancer were older at the time of their ovarian cancer diagnoses ($p = 0.001$) and were less likely to have been diagnosed with localized disease ($p = 0.05$). The tumor histologies were similar for the two groups of women ($p = 0.10$).

Table 2 shows observed and expected numbers of deaths for the 824 White women diagnosed with ovarian cancer and prior breast cancer, by age at ovarian cancer diagnosis. The expected numbers are based on the death rates in White women with ovarian cancer only, adjusted for ovarian cancer stage. Overall, the observed number of deaths from ovarian cancer among women with prior breast cancer was significantly less than expected ($p = 0.001$). This deficit was statistically significant in each of the three age groups spanning the age range from 55 to 84 years. Table 3 shows observed and expected numbers of ovarian cancer deaths among the 824 White women diagnosed with ovarian cancer and prior breast cancer, by ovarian cancer stage.

The expected numbers are based on the death rates in White women with ovarian cancer only, adjusted for age at ovarian cancer diagnosis. The observed number of deaths was significantly lower than expected, in all women and in women diagnosed with advanced ovarian cancer. Differences between the number of observed and expected deaths did not achieve statistical significance at the other stages.

Figure 1 shows stage-specific survival probabilities for the two groups of women. Overall, the estimated 5-year survival probability for women with a prior breast cancer was 49 percent (95 percent confidence interval (CI): 45, 56), compared with a corresponding probability of 45 percent among women without prior breast cancer (95 percent CI: 44, 46). The 5-year survival advantage for patients with a prior breast cancer was most pronounced in women diagnosed with distant disease at ages 55 years and older. The 5-year survival for women with breast cancer was 32 percent (95 percent CI: 26, 38) compared with a corresponding probability of 20 percent for women without breast cancer (95 percent CI: 19, 21). Adjustment for age and stage of disease at ovarian cancer diagnosis supported this survival advantage: the age- and stage-adjusted death rate ratio comparing women with and without prior breast cancer was 0.75 (95 percent CI: 0.68, 0.84). Adjustment for geographic area did not significantly affect the death rate ratios.
TABLE 2. Observed and expected numbers of deaths among White epithelial ovarian cancer patients with prior history of breast cancer, by age at ovarian cancer diagnosis, SEER* registries, 1973–1995

<table>
<thead>
<tr>
<th>Age at diagnosis (years)</th>
<th>No. of subjects</th>
<th>Person-years of follow-up</th>
<th>Observed no. of deaths</th>
<th>Expected no. of deaths†</th>
<th>p value</th>
<th>Death rate‡ ratio</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>3</td>
<td>22.0</td>
<td>1</td>
<td>1.1</td>
<td>0.990</td>
<td>0.91</td>
<td>0.04, 5.06</td>
</tr>
<tr>
<td>35–44</td>
<td>37</td>
<td>162.3</td>
<td>17</td>
<td>14.4</td>
<td>0.500</td>
<td>1.18</td>
<td>0.68, 1.89</td>
</tr>
<tr>
<td>45–54</td>
<td>117</td>
<td>466.0</td>
<td>48</td>
<td>41.6</td>
<td>0.350</td>
<td>1.15</td>
<td>0.82, 1.53</td>
</tr>
<tr>
<td>55–64</td>
<td>219</td>
<td>825.5</td>
<td>71</td>
<td>91.9</td>
<td>0.025</td>
<td>0.77</td>
<td>0.58, 0.97</td>
</tr>
<tr>
<td>65–74</td>
<td>231</td>
<td>601.7</td>
<td>99</td>
<td>135.0</td>
<td>0.005</td>
<td>0.73</td>
<td>0.58, 0.89</td>
</tr>
<tr>
<td>75–84</td>
<td>175</td>
<td>342.0</td>
<td>84</td>
<td>111.0</td>
<td>0.001</td>
<td>0.76</td>
<td>0.59, 0.94</td>
</tr>
<tr>
<td>≥85</td>
<td>42</td>
<td>45.0</td>
<td>25</td>
<td>31.2</td>
<td>0.250</td>
<td>0.80</td>
<td>0.51, 1.18</td>
</tr>
<tr>
<td>Total</td>
<td>824</td>
<td>2,464.5</td>
<td>345</td>
<td>426.2§</td>
<td>0.001</td>
<td>0.75</td>
<td>0.68, 0.84</td>
</tr>
</tbody>
</table>

* SEER, Surveillance, Epidemiology, and End Results; CI, confidence interval.
† Due to ovarian cancer, based on death rates in ovarian cancer patients without a prior breast cancer, adjusted for stage at ovarian cancer diagnosis.
‡ Adjusted for stage at ovarian cancer diagnosis.
§ Adjusted for age and stage of disease at diagnosis.

DISCUSSION

These population-based data suggest that, among White women diagnosed with invasive epithelial ovarian cancer, those with a prior history of breast cancer survive their ovarian cancer longer than do women without such a history. Although BRCA1 mutation status was not available for these women, it has been estimated that 88 percent of women with both breast and ovarian cancers are BRCA1 mutation carriers (12) compared with 5 percent of all ovarian cancer patients (4, 13). Thus, the data provide indirect support for the hypothesis that BRCA1 heterozygote ovarian cancer patients have better prognosis than do other ovarian cancer patients.

Several strengths and limitations of this analysis warrant discussion. One strength is that the comparison is based on a population-based surveillance system and, thus, is free from the potential selection bias pertinent to some of the other studies addressing the issue. These latter studies compared survival of BRCA1 heterozygote patients who were identified because they had been attending a high-risk clinic with survival of patients identified in some other setting. Individuals attending high-risk clinics tend to have closer surveillance, which could lead to earlier detection and spuriously improved survival (i.e., “lead time bias”).

A second strength arises because, unlike most of the previous analyses, we did not rely on mutation testing of archived paraffin-embedded tissue, a procedure that can lead to spurious BRCA1 “mutations” (18). Such spurious mutations would blur the distinction between BRCA1 heterozygotes and nonheterozygotes, leading to failure to detect a survival difference.

This strength is counterbalanced, however, by the potential for a different form of misclassification in the present analysis. Some of the patients classified as having no prior breast cancer may have been diagnosed with the disease while residing outside the SEER catchment area. Such misclassification would decrease the chance of finding a survival difference and would bias the death rate ratio toward unity. However, the death rate ratio was significantly reduced and the magnitude of the effect may have been underestimated.

TABLE 3. Observed and expected numbers of deaths among White epithelial ovarian cancer patients with a prior history of breast cancer, by stage at ovarian cancer diagnosis, SEER* registries, 1973–1995

<table>
<thead>
<tr>
<th>Stage at diagnosis</th>
<th>No. of subjects</th>
<th>Person-years of follow-up</th>
<th>Observed no. of deaths</th>
<th>Expected no. of deaths†</th>
<th>p value</th>
<th>Death rate‡ ratio</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>152</td>
<td>852.3</td>
<td>16</td>
<td>16.0</td>
<td>0.990</td>
<td>1.00</td>
<td>0.56, 1.62</td>
</tr>
<tr>
<td>Regional</td>
<td>114</td>
<td>432.3</td>
<td>43</td>
<td>50.1</td>
<td>0.300</td>
<td>0.86</td>
<td>0.61, 1.16</td>
</tr>
<tr>
<td>Distant</td>
<td>499</td>
<td>1,060.5</td>
<td>257</td>
<td>329.2</td>
<td>0.001</td>
<td>0.78</td>
<td>0.67, 0.88</td>
</tr>
<tr>
<td>Unstaged</td>
<td>59</td>
<td>119.4</td>
<td>29</td>
<td>30.9</td>
<td>0.700</td>
<td>0.94</td>
<td>0.62, 1.08</td>
</tr>
<tr>
<td>Total</td>
<td>824</td>
<td>2,464.5</td>
<td>345</td>
<td>426.2§</td>
<td>0.001</td>
<td>0.75</td>
<td>0.68, 0.84</td>
</tr>
</tbody>
</table>

* SEER, Surveillance, Epidemiology, and End Results; CI, confidence interval.
† Due to ovarian cancer, based on death rates in ovarian cancer patients without a prior breast cancer, adjusted for age at ovarian cancer diagnosis.
‡ Adjusted for age at diagnosis.
§ Adjusted for age and stage of disease at diagnosis.
A second limitation of the present analysis is the absence of data on clinical prognostic factors for ovarian cancer survival, such as the extent of tumor before and after surgery, and the type of chemotherapy. If patients with a prior breast cancer receive more optimal debulking or more effective chemotherapy than do patients without such a prior cancer, our inability to adjust for the differences could mislead us to erroneously interpret the observed differences as biologically based.

A third limitation of the study is the lack of information on ovarian cancer screening history. Breast cancer patients may be screened more aggressively for ovarian cancer than women in the general population, which might cause earlier than usual detection of the disease and improved survival.

Three other studies have reported improved ovarian cancer survival in BRCA1 carriers. Rubin et al. (6) estimated the median survival of 43 BRCA1-heterozygote patients with advanced disease to be 77 months, compared with 29 months in control patients matched for age, tumor stage, histology, and grade. In a second study, the 5-year survival rate for 13 Japanese BRCA1 heterozygotes with stage III ovarian cancer was 79 percent, compared with a rate of 30 percent for 29 stage III patients who were deemed “sporadic” (criteria unknown) and who were matched to BRCA1-positive patients on age and treatment type at diagnosis (7). These two studies have several limitations. BRCA1 mutation status was determined using archived tissue, although the Japanese study did identify some BRCA1 carriers with DNA from blood lymphocytes. The BRCA1 heterozygotes were identified through high-risk clinics, leading to possible selection bias. Rubin et al. (6) were unable to control for the extent of disease and type of treatment, since several of the BRCA1 heterozygotes had been diagnosed many years ago.

The third study reporting improved survival in BRCA1 carriers included 933 consecutive cases diagnosed with epithelial ovarian cancer from a single institution (8). The median 5-year survival for 67 advanced stage BRCA1 ovarian cancer patients was significantly longer than that of matched ovarian cancer patients without BRCA1 mutations. Interestingly, the authors found that BRCA1-heterozygote patients received optimal debulking more frequently than did patients without BRCA1 mutations. The strengths of this study include selection of consecutive cases from a single institution and more detailed information on the extentiveness of disease and the type of chemotherapy. As with the two previous studies, BRCA1 mutation status was determined using archived tissue.

In contrast to these results, three studies have found no survival differences in BRCA1 mutation carriers compared with either patients who tested BRCA1 negative or untested patients in the general population. Pharaoh et al. (9) reported that the 5-year survival in 127 ovarian cancer patients from multiple-case families segregating BRCA1 mutations was similar to that of 119 patients from families testing negative for BRCA1 mutations. A strength of this study is its use of DNA from peripheral lymphocytes to determine BRCA1 mutation status. The survival similarity is noteworthy in view of the fact that the patients from BRCA1-positive families were more likely than those from BRCA1-negative families to be diagnosed with stage III/IV disease (89 percent vs. 65 percent).

In a second study, Johannsson et al. (10) compared survival among 38 Swedish BRCA1-positive ovarian cancer
patients with that of 97 ovarian cancer patients from the general Swedish population, matched to the \textit{BRCA1} heterozygotes on age, stage of disease at diagnosis, and calendar year of diagnosis. \textit{BRCA1} carriers were those who tested positive in analysis of either lymphocytes or archived tissue, or those deemed to be obligate carriers. The death rate ratio was 1.2 (95 percent CI: 0.5, 2.8).

Finally, Lee et al. (11) compared ovarian cancer survival among 10 first-degree relatives of US Ashkenazi Jewish carriers of \textit{BRCA1} or \textit{BRCA2} mutations with that of 116 ovarian cancer patients who were first-degree relatives of Ashkenazi Jewish noncarriers. They found similar survival in the two groups of relatives.

These latter three studies share some of the limitations discussed earlier. In particular, results from the first two studies are based on \textit{BRCA1}-heterozygote patients participating in high-risk clinics. None of them controlled for extent of disease or type of treatment. It is also possible that inconsistencies among the positive and negative findings reflect survival differences in carriers of different site-specific \textit{BRCA1} mutations in different populations.

A survival advantage for \textit{BRCA1}-heterozygote ovarian cancer patients, if not due to chance or bias, may reflect their better response to chemotherapy (8). If the \textit{BRCA1} protein plays a role in DNA repair (19), then \textit{BRCA1}-deficient cancer cells may be unable to repair the DNA damage induced by chemotherapeutic agents and thus are killed by the treatment. Further studies are needed to address this issue.

\textbf{REFERENCES}