Ovarian Cancer Risk in Ashkenazi Jewish Carriers of \textit{BRCA1} and \textit{BRCA2} Mutations

Jaya M. Satagopan,\textsuperscript{1,2} Jeff Boyd, Noah D. Kauff, Mark Robson, Lauren Scheuer, Steven Narod, and Kenneth Offit


ABSTRACT

\textbf{Purpose:} Several studies to date have reported ovarian cancer risk due to inherited \textit{BRCA1} and \textit{BRCA2} mutations using familial data or population-based series of probands. Familial aggregation associated with both of these methods may result in a substantial ascertainment bias. To address this, we have used a case-control design that does not involve familial aggregation to estimate the lifetime penetrance of ovarian cancer due to \textit{BRCA1} and \textit{BRCA2} mutations.

\textbf{Experimental Design:} A total of 382 ovarian cancer cases self-identified as being Jewish with no prior diagnosis of breast cancer were derived from two hospital-based series. In the first series, all 197 invasive epithelial ovarian cancer cases self-identified as Jewish and without a prior history of breast cancer, diagnosed and treated at Memorial Sloan-Kettering Cancer Center between 1986 and 2000, were identified. In the second series, 185 Jewish invasive epithelial ovarian cancer patients without prior breast cancer were identified in a study conducted at 11 centers in North America and Israel from 1995 to 1996. Controls were 3434 Jewish women without any prior history of breast or ovarian cancer from a large study of genotyped volunteers of Jewish origin in the Washington, D. C. area recruited by investigators at the National Cancer Institute. The cases and controls were genotyped for three Ashkenazi Jewish founder mutations, namely \textit{BRCA1} mutations in 185delAG and 5382insC and \textit{BRCA2} mutations in 6174delT.

The lifetime penetrances were estimated using the odds ratios, mutation prevalence in the controls, and ovarian cancer incidence rates in the general American population obtained from the Surveillance, Epidemiology and End Results database adjusted for the incidence of ovarian cancer following breast cancer.

\textbf{Results:} Mutations were identified in 147 cases and 62 controls. The estimated penetrances at age 70 years were 37\% (95\% confidence interval, 25–71\%) for a \textit{BRCA1} mutation and 21\% (95\% CI, 13–41\%) for a \textit{BRCA2} mutation.

\textbf{Conclusions:} The lifetime penetrances of \textit{BRCA1} mutations are lower than estimates obtained using familial data with multiple affected members but larger than estimates from some population-based proband series. The lifetime penetrance estimate of a \textit{BRCA2} mutation is in the range reported by some of the studies based on familial data. These results could have implications for clinical counseling, surgical interventions, and screening recommendations in women carrying these founder mutations.

INTRODUCTION

Ovarian cancer is a leading cause of cancer-related mortality among women in the United States. The SEER\textsuperscript{3} lifetime risk of ovarian cancer is 1.71\% (1). It is well known that mutations in the \textit{BRCA1} and \textit{BRCA2} genes account for a large number, but not all, of familial ovarian cancers (2). Inherited mutations commonly found in Ashkenazi Jewish individuals (namely, 185delAG and 5382insC in \textit{BRCA1} and 6174delT in \textit{BRCA2}) have been of particular interest. Several studies to date have reported lifetime risk of ovarian cancer due to inherited \textit{BRCA1} and \textit{BRCA2} mutations using familial data and population series of ovarian cancer probands. The lifetime risks are estimated in the range of 28–66\% for a \textit{BRCA1} mutation (2–8) and 16–27\% for a \textit{BRCA2} mutation (5, 9).

In studies involving family-based ascertainment, families with a high cancer incidence are more likely to be identified than families with no or fewer cancers among the relatives of probands. As a result, this can lead to a substantial positive bias in the risk estimates. Even population-based studies that rely on occurrences of cancer in relatives of probands to estimate penetrance can be biased if incident cases are used as probands (10).

We recently used a case-control design to estimate the lifetime risk of breast cancer conferred by inherited \textit{BRCA1} and \textit{BRCA2} mutations among Ashkenazi Jewish women (11). In this design familial aggregation is not used, eliminating ascertainment bias. We showed that the lifetime risk of breast cancer due to an inherited mutation is substantially lower than the estimates reported in family-based studies. The goal of this study is to investigate the lifetime risk of ovarian cancer due to an inherited \textit{BRCA1} or \textit{BRCA2} mutation among Ashkenazi Jewish women ascertained using the same case-control approach and compare the estimates with those obtained by family-based and population-based studies.

\textsuperscript{3}The abbreviations used are: SEER, Surveillance, Epidemiology and End Results; CI, confidence interval; MSKCC, Memorial Sloan-Kettering Cancer Center; OCCR, ovarian cancer cluster region.
MATERIALS AND METHODS

Cases. Cases were derived from two hospital-based ascertainment series: the first series was from MSKCC, New York (12); and the second series was from 11 centers in North America and Israel (13). The first series comprised of 1150 consecutive ovarian cancer cases diagnosed and treated at MSKCC between 1986 and 2000. A subset of this series has been reported previously (12). Review of patient records identified a total of 228 patients with ovarian cancer who identified themselves as being Ashkenazi Jewish. Of these, 31 patients had a prior history of breast cancer. Archival pathological tissue specimens were obtained from the hospital tissue bank for each of these participants. Once the ethnicity of the participants, overall survival time, and other clinical factors were determined, the samples were anonymized following published guidelines (14). Samples were then analyzed to determine the presence of 185delAG and 5382insC BRCA1 or 6174delT BRCA2 mutations using previously published methods (12). The second series comprised of ovarian cancer cases from 11 centers in North America and Israel, as reported by Moslehi et al. (13). Ovarian cancer patients, self-reported as Jewish, were contacted to participate in a study of mutation analysis of BRCA1 and BRCA2 genes. A total of 465 ovarian cancer cases of Jewish origin were identified, of whom 208 cases were alive. These 208 individuals were pathologically confirmed to have invasive epithelial ovarian cancer, agreed to participate in the mutation analysis study, and provided blood samples. Twenty-three of these 208 ovarian cancer patients had a prior history of breast cancer. Aggregating data from these two series gave a total of 436 Ashkenazi Jewish ovarian cancer patients, of whom 382 cases did not have a prior history of breast cancer.

Controls. The controls required for this study were obtained from a study of genotyped volunteers in the Washington, D. C. area (15), providing a large series of Jewish individuals without a history of breast or ovarian cancer at the time of ascertainment. Jewish volunteers, both men and women, were recruited through advertisements. Breast and ovarian cancer history of the volunteers and their families was obtained. Furthermore, blood samples were obtained from all of the volunteers. A total of 3434 women without a personal history of breast or ovarian cancer at the time of data collection were recruited through advertisements. Breast and ovarian cancer at the time of data collection were included in the analysis. Penetrance estimation calculations were provided in the “Appendix.” This approach is similar to the estimation method described in our breast cancer penetrance study (11). Briefly, the lifetime risk in a given age group can be estimated as a function of the following three quantities: (a) SEER ovarian cancer incidence rate after adjusting for the SEER incidence of ovarian cancer in patients with a prior diagnosis of breast cancer in that age group, and the SEER breast cancer incidence in that age group; (b) the age-specific relative risk of the mutation; and (c) the age-specific carrier prevalence of the mutation. This calculation involves the following three assumptions: (a) the hospital-based series of Jewish ovarian cancer cases are representative of the general population series of Jewish cases; (b) the controls are representative of the general Jewish population; and (c) the breast and ovarian cancer incidence rates among the Jewish population without BRCA mutation is similar to the SEER breast and ovarian cancer incidence rate. The CIs of the lifetime risk estimates were calculated using the bootstrap method (16). This involves repeatedly calculating penetrance estimates by sampling cases and controls with replacement from the observed data and deriving the CIs from the empirical distribution of the penetrance estimates.

The risk conferred by BRCA1 versus BRCA2 mutations and the risk conferred by 185delAG versus 5382insC BRCA1 mutations were compared using a logistic regression model restricted to mutation carriers (11). The outcome was case-control status. The variables entered into the model were the mutation BRCA1 versus BRCA2 (or 185delAG versus 5382insC) and age. A likelihood ratio test was then used to test the hypothesis of no difference in the risk conferred by the two mutations.

RESULTS

Aggregating the two case series and restricting to only cases without a prior diagnosis of breast cancer provided a total of 382 incident ovarian cancer cases. A BRCA1 mutation was observed in 103 (27%) cases, and 44 (12%) cases had a BRCA2 mutation. Table 1 gives the age-specific frequencies of cases and controls and the corresponding mutation rates. The age-specific relative risks of BRCA1 and BRCA2 mutations are given in Table 2. Relative risks corresponding to an inherited BRCA1 mutation were estimated to be 42.4 in the <40 age group, 90.8 in age group 40–49, and 53.0 in the ≥50 age group. The corresponding relative risks due to an inherited BRCA2 mutation were estimated as 6.5, 14.9, and 29.7, respectively.

Table 3 gives the age-specific SEER ovarian cancer incidence rates in the general population, adjusted for the incidence of breast cancer in the corresponding age groups. These adjusted rates, the age-specific relative risks, and carrier mutation prevalence were used to derive the age-specific lifetime risk estimates given in Table 4. The estimated lifetime risk of ovarian cancer at age 70 was 37% (95% CI, 25–71%) due to an inherited BRCA1 mutation and 21% (95% CI, 13–41%) due to an inherited BRCA2 mutation. Based on the likelihood ratio test, the risk conferred by a BRCA1 mutation is significantly higher than the risk conferred by a BRCA2 mutation (P = 0.01).

These analyses were repeated for 185delAG and 5382insC BRCA1 mutations (Table 5). However, it must be noted that very few cases and controls carry a 5382insC mutation. The estimated lifetime risks were 66% (95% CI, 37–100%) due to a 185delAG mutation and 29% (95% CI, 16–69%) due to a
5382insC mutation. There was no significant difference between the risks conferred by these \textit{BRCA1} mutations ($P = 0.38$).

\textbf{DISCUSSION}

The lifetime risk estimate for \textit{BRCA1} was lower than estimates from familial studies (3, 4) but larger than estimates from some of the population-based studies (6, 9). The lifetime risk of \textit{BRCA2} mutation was in the range of 16–27% reported in two family studies (4, 5). The penetrance estimates reported here represent the risk of ovarian cancer in the absence of any risk of prior breast cancer. A total of 54 ovarian cancer cases with a prior diagnosis of breast cancer were excluded from our analysis. Of the 54 cases, 25 had a 185delAG mutation, 5 had a 5382insC mutation, and 9 had a 6174delT \textit{BRCA2} mutation. The remaining 15 cases did not carry any of these three mutations.

The lifetime risks were estimated based on three major assumptions: (a) the hospital-based cases are representative of the population of ovarian cancer cases; (b) the volunteer controls are representative of the general Ashkenazi Jewish population; and (c) the cancer incidence in the general Ashkenazi Jewish population without \textit{BRCA} mutations is similar to the...
controls had a
the true penetrance figures would actually be higher. A total of
odds ratios derived in our analysis would be underestimates, and
contained an enriched proportion of mutation carriers, then the
lyzing genetic influence on cancer risk. If the control group
family history were more likely to participate in a study ana-
targeted media outlets. It is likely that individuals with a strong
series of volunteers recruited via both general and Jewish-

ovarian cancer cases (12). The controls were derived from a
nosed and treated at MSKCC were similar to those of sporadic
i.e., BRCA
features of high-risk (linked) cancer patients diag-

more, previous analysis showed that the clinicopathological
ovarian cancer case population in the United States. Further-
SEER rate. The cases were derived from a hospital-based series of
ovarian cancer patients. Because initial management of ovarian
cancer in the United States is predominantly surgical, cases from
the MSKCC series are likely to be similar to the general
population and the incidence of second primary ovarian cancer
following a first primary breast cancer. Violation of this assump-
tion would lead to biased risk estimates. Therefore, a
sensitivity analysis was performed to determine lifetime risk
when the Jewish population had 10% higher risk than the SEER
population and the incidence of second primary ovarian cancer

mutation frequency is similar to the 2.2% reported in the study of
general Ashkenazi Jewish population (17), suggesting that the
mutation prevalence is not inflated among these controls. The
SEER ovarian cancer incidence rates were assumed to the
data from 60 families. Mutations near the 5’ end of the coding
region are thought to confer a higher risk than mutations near

**Table 4** Age-stratified analysis of lifetime risk of ovarian cancer

<table>
<thead>
<tr>
<th>BRCA1</th>
<th>SEER adjusted incidence rate</th>
<th>Carrier prevalence</th>
<th>Relative risk</th>
<th>Carrier incidence rate</th>
<th>Penetrance (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–29 yrs</td>
<td>0.0004</td>
<td>0.016</td>
<td>42.4</td>
<td>0.010</td>
<td>1% (0–2%)</td>
</tr>
<tr>
<td>30–39 yrs</td>
<td>0.0008</td>
<td>0.016</td>
<td>42.4</td>
<td>0.020</td>
<td>3% (1–7%)</td>
</tr>
<tr>
<td>40–49 yrs</td>
<td>0.0017</td>
<td>0.019</td>
<td>90.8</td>
<td>0.080</td>
<td>11% (7–21%)</td>
</tr>
<tr>
<td>50–59 yrs</td>
<td>0.0032</td>
<td>0.006</td>
<td>53.0</td>
<td>0.132</td>
<td>23% (16–44%)</td>
</tr>
<tr>
<td>60–69 yrs</td>
<td>0.0045</td>
<td>0.006</td>
<td>53.0</td>
<td>0.185</td>
<td>37% (25–71%)</td>
</tr>
<tr>
<td>70–79 yrs</td>
<td>0.0058</td>
<td>0.006</td>
<td>53.0</td>
<td>0.240</td>
<td>52% (35–90%)</td>
</tr>
<tr>
<td>80+ yrs</td>
<td>0.0057</td>
<td>0.006</td>
<td>53.0</td>
<td>0.233</td>
<td>63% (44–96%)</td>
</tr>
</tbody>
</table>

**Table 5** Age-stratified analysis of lifetime risk of ovarian cancer associated with BRCA1 mutations

<table>
<thead>
<tr>
<th>185delAG</th>
<th>SEER adjusted incidence rate</th>
<th>Carrier prevalence</th>
<th>Relative risk</th>
<th>Carrier incidence rate</th>
<th>Penetrance (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–29 yrs</td>
<td>0.0004</td>
<td>0.013</td>
<td>46.0</td>
<td>0.011</td>
<td>1% (0–4%)</td>
</tr>
<tr>
<td>30–39 yrs</td>
<td>0.0008</td>
<td>0.013</td>
<td>46.0</td>
<td>0.022</td>
<td>3% (1–8%)</td>
</tr>
<tr>
<td>40–49 yrs</td>
<td>0.0017</td>
<td>0.008</td>
<td>84.8</td>
<td>0.087</td>
<td>12% (7–25%)</td>
</tr>
<tr>
<td>50–59 yrs</td>
<td>0.0032</td>
<td>0.002</td>
<td>117.9</td>
<td>0.311</td>
<td>39% (23–100%)</td>
</tr>
<tr>
<td>60–69 yrs</td>
<td>0.0045</td>
<td>0.002</td>
<td>117.9</td>
<td>0.436</td>
<td>66% (37–100%)</td>
</tr>
<tr>
<td>70–79 yrs</td>
<td>0.0058</td>
<td>0.002</td>
<td>117.9</td>
<td>0.565</td>
<td>85% (53–100%)</td>
</tr>
<tr>
<td>80+ yrs</td>
<td>0.0057</td>
<td>0.002</td>
<td>117.9</td>
<td>0.549</td>
<td>93% (63–100%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5382insC</th>
<th>SEER adjusted incidence rate</th>
<th>Carrier prevalence</th>
<th>Relative risk</th>
<th>Carrier incidence rate</th>
<th>Penetrance (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–29 yrs</td>
<td>0.0004</td>
<td>0.003</td>
<td>25.9</td>
<td>0.010</td>
<td>1% (0–5%)</td>
</tr>
<tr>
<td>30–39 yrs</td>
<td>0.0008</td>
<td>0.003</td>
<td>25.9</td>
<td>0.019</td>
<td>3% (0–14%)</td>
</tr>
<tr>
<td>40–49 yrs</td>
<td>0.0017</td>
<td>0.003</td>
<td>109.0</td>
<td>0.146</td>
<td>17% (6–55%)</td>
</tr>
<tr>
<td>50–59 yrs</td>
<td>0.0032</td>
<td>0.004</td>
<td>20.6</td>
<td>0.062</td>
<td>22% (11–60%)</td>
</tr>
<tr>
<td>60–69 yrs</td>
<td>0.0045</td>
<td>0.004</td>
<td>20.6</td>
<td>0.087</td>
<td>29% (16–69%)</td>
</tr>
<tr>
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</tr>
<tr>
<td>80+ yrs</td>
<td>0.0057</td>
<td>0.004</td>
<td>20.6</td>
<td>0.109</td>
<td>44% (29–86%)</td>
</tr>
</tbody>
</table>

*a* The adjusted incidence rates (R̂ a*) from Table 3.
*b* Penetrance is the probability of a mutation carrier developing ovarian cancer by the end of the age interval.
the 3’ end. The 185delAG mutation is located near the 5’ end, and the 5382insC mutation is located near the 3’ end of the BRCA1 coding region. Our estimate of a higher penetrance associated with a 185delAG mutation than a 5382insC mutation, although not statistically significant, is consistent with these findings.

The penetrance of BRCA2 mutation has not been widely reported. Our results show that a BRCA2 mutation is not a significant risk factor in younger women (age <40 years; odds ratio, 6.5; 95% CI, 0.8–55.6). The odds ratio increases as the population ages, suggesting BRCA2 to be a risk factor only in older women. The 6174delT mutation is located in the OCR (19), in the region of exon 11 extending from nucleotide 3035 to 6629. Truncating mutations in OCR are known to be associated with an increased risk of breast and ovarian cancer (5, 19). Furthermore, founder mutations in BRCA1 are believed to have a significantly higher penetrance than a founder mutation in BRCA2 (20). Our results are consistent with the findings of these published studies. Recent studies have reported associations between other cancers such as colorectal, stomach, pancreatic, and prostate cancers and mutations in BRCA1 and OCR BRCA2 mutations (2, 5, 9, 13, 21, 22).

Our penetrance estimates can have implications for the management of ovarian cancer in germ-line mutation carriers. Prophylactic mastectomy and oophorectomy may be reasonable options for germ-line BRCA1 and BRCA2 mutation carriers. Their advantages have been reported in recent literature (23–26). The penetrance estimates derived in this study can be used in decisions regarding such preventive measures (i.e., risk-reducing oophorectomy might safely be delayed until after menopause in carriers of the 6174delT BRCA2 mutation). Surgical removal of the ovaries is increasingly offered to BRCA mutation carriers, given the variable sensitivity of ovarian cancer screening strategies and the finding of early stage tumors in “prophylactic” oophorectomy specimens (27). In the absence of more sensitive means of detecting ovarian cancer, penetrance estimates such as those provided here will continue to be used to inform surgical as well as medical interventions in populations at greatest hereditary risk for ovarian cancer.

ACKNOWLEDGMENTS

We thank Dr. Colin Begg for providing the standardized incidence ratios and insightful comments. The control data were obtained from Dr. Jeff Stratton and colleagues from the National Cancer Institute.

Appendix

Penetrance Estimate. The penetrance of ovarian cancer in mutation carriers at a given age is the probability of developing ovarian cancer by that age in a randomly selected individual, assuming that the individual does not die of competing causes of risk before that age. Denote \( I_{a1}, I_{a2}, \ldots \) as the age-specific incidence of ovarian cancer among carriers without a prior history of breast cancer in age groups 1, 2, . . . . The penetrance \( P_a \) at the end of the \( a^{th} \) age interval can be written as shown below.

\[
P_a = 1 - [(1 - I_{a0})(1 - I_{a1}) \cdots (1 - I_{an})]
\]

The age-specific carrier incidence in the \( a^{th} \) age group, \( I_{ao} \), can be calculated as a function of the following three quantities:

(a) the general population incidence rate of ovarian cancer without a prior history of breast cancer in the \( a^{th} \) age group, denoted \( R_a^* \) (referred to as the age-specific adjusted ovarian cancer incidence rate); (b) the age-specific mutation prevalence, denoted \( \pi_a \); and (c) the age-specific relative risk of the mutation, denoted \( \phi_a \).

The overall incidence of ovarian cancer for a given age group in the general population is the weighted average of ovarian cancer incidence with and without a prior history of breast cancer, weighted by the (competing risk of) breast cancer incidence in the general population in that age group. Furthermore, the ovarian cancer incidence among those without a prior history of breast cancer in the general population is a weighted average of the incidence among carriers and noncarriers without breast cancer, weighted by the mutation prevalence. For the \( a^{th} \) age group, denote \( I_a \) as the general population incidence of ovarian cancer, \( S_a^* \) as the incidence of (second primary) ovarian cancer among (first primary) breast cancer cases, and \( F_a \) as the incidence of breast cancer in the general population. Then, the age-specific adjusted ovarian cancer incidence rate is given by:

\[
R_a^* = \frac{(1 - S_a^* F_a)(1 - F_a)}{1 - F_a} \]

The age-specific carrier incidence rate \( I_{ao} \) can then be written as:

\[
I_{ao} = R_a^* \phi_a \pi_a (1 - \pi_a)
\]

In practice, the quantity \( S_a^* \) can be obtained as a product of the age-specific standardized incidence ratio of ovarian cancer in breast cancer cases and the age-specific incidence of ovarian cancer in the general population.

REFERENCES


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