Estimating survival rates after ovarian cancer among women tested for BRCA1 and BRCA2 mutations


Several studies have reported that women with ovarian cancer and a BRCA1 or BRCA2 mutation have better survival than women with ovarian cancer and no mutation. Potential reasons for this include possible differences in histologic subtype, stage, grade and response to chemotherapy, but some of the difference in survival may be due to systematic bias, i.e. a difference in survival rates for women who do and who do not undergo genetic testing. We estimated the survival rate in 1423 ovarian cancer patients from Ontario who had genetic testing and compared this with the survival rate for all 3367 ovarian cancer patients from the province from whom the tested sample was derived. Tested women had a 10-year survival of 54.5%, compared to 35.8% for all patients in the province. We evaluated the extent to which three different methods of adjustment eliminated the observed difference. The adjusted rates for the tested cohort were closer to the provincial average, but each adjustment method resulted in a modest over-estimate of 10-year survival, ranging from 6.1% to 10.0%. The mortality advantage for tested women was due, in part, to a lower than expected mortality rate of tested women in the period following genetic testing.

Conflict of interest

None of the authors declare a conflict of interest.
have genetic testing will be 2-year survivors. In reality, the time from diagnosis until testing varies widely in clinical practice. A second possibility is that even if they are alive, women who are ill may be less likely to get tested than women who are cured of cancer, or in remission. This may be more important for women who are offered genetic testing in the context of a research program than for women who offered genetic testing in a clinical setting. If this were the case, then we would expect the mortality rate of tested women to be lower than expected in the immediate aftermath of a genetic test. In light of these considerations, survival estimates based solely on tested women may overestimate the true survival of the underlying population to some extent and it may be misleading to counsel women with a mutation based on these crude survival rates. Many investigators have acknowledged the first possibility (survivorship bias) and as a result, different adjustments for survivorship bias have been made. For example, Bolton et al. (9) used left-truncated survival analysis to account for the variable time from diagnosis until genetic testing. A second approach, taken by Ra and colleagues, was to exclude cases if the delay from diagnosis until genetic testing exceeded 2 years. Those included in the study were considered to be ‘incident’ cases. It is also possible to adjust for survivorship by calculating the annual mortality rates for each year from diagnosis and then constructing theoretical survival curves based on these point estimates (incidence density approach).

In Ontario, we have access to a provincial database of ovarian cancer patients which includes data on survival. For the years of the current study (1995–1999 and 2002–2004), all 3653 Ontario residents diagnosed with invasive epithelial ovarian cancer were included in the database. Of these, 1423 women (39%) underwent genetic testing in the context of a province-wide research study (1). We have a unique opportunity to compare the mortality rates in the genetic-tested population with that of the underlying Ontario population. We may also evaluate the extent to which adjusting for survivorship from diagnosis to testing, using the three methods described above, is effective in reducing the survivorship bias.

**Subjects and methods**

All patients in the province of Ontario, Canada, diagnosed from January 1995 through December 1999 and 2002–2004 with invasive epithelial ovarian cancers were identified by monitoring acquisitions of the Ontario Cancer Registry. Patients were between 20 and 79 years of age and were residents in Ontario at the time of diagnosis of a new primary epithelial ovarian tumor. Of the 3653 total cases, 286 were excluded because of missing information on key variables. All were eligible for genetic testing, and of 3367 eligible cases, genetic testing was accomplished on 1423. The remaining cases were not tested for a variety of reasons: for 1081 cases, the patient had died before contact was made; other reasons for non-participation included subject refusal (216 cases), subject too ill (137 cases), physician refusal (150 cases), did not return blood kit (159 cases), language barrier (68 cases), not able to contact case’s physician (25 cases), and inability to locate (108 cases). Of the 1423 cases that participated in the study, the mean time elapsed from date of diagnosis to date of blood draw was 23.1 months (range 0.1–79 months). The results of the genetic testing are described elsewhere (1).

**Survival**

We estimated the 10-year survival for the underlying cohort and for the two sub-cohorts who did and who did not have genetic testing. We conducted an unadjusted Kaplan–Meier survival analysis on the entire cohort and sub-cohorts from the date of diagnosis until date of death from ovarian cancer or September 2010. Subsequently, in order to account for the time elapsed between the date of diagnosis and the date of ascertainment (genetic testing), we performed three different adjusted analyses. In the first analysis, we excluded patients for whom two or more years had elapsed from the date of diagnosis until the date of genetic testing. This analysis was then repeated replacing the 2-year time interval with a 3-year interval and then with a 1-year interval.

In the second adjustment, we calculated annual mortality rates specifically for each single year time period from diagnosis until 10 years after diagnosis. For each 1-year interval we calculated the number of person-years of exposure for members of the cohort and the number of deaths from ovarian cancer in the 1-year interval. The annual rate was estimated as the ratio of number of observed deaths to number of person-years in that interval. We then used these point estimates (incidence densities) to construct the hypothetical survival experience of a theoretical cohort of at-risk women.

The third adjustment was done using a left-truncated survival analysis implemented in SAS®. In this analysis, each woman only contributes person-years from the time of ascertainment (i.e. genetic testing). To evaluate the validity of the left-truncated survival analysis as implemented in SAS, we simulated a cohort of genetically tested women, based on the original entire cohort of 3367 women. For each of the 3367 women, we assigned a random (simulated) date of genetic testing, ranging from zero to 36 months from the date of diagnosis (based on a random number generator assuming a uniform distribution). The survival of the simulated-tested cohort was then estimated from the date of diagnosis using the left-truncated approach. The actual survival curve and the adjusted survival curve from the simulated-tested cohort were then compared.

**Results**

For the entire cohort, the 5-year actuarial survival, based on the Kaplan–Meier method, was 45.6% and
the 10-year survival rate was 35.8%. As much as 1423 women had a genetic test, at a mean of 23.1 months from diagnosis (range 0.1–79 months). The crude survival from diagnosis was much greater for the tested cases than for the untested cases (Fig. 1). The 10-year survival for the tested cases was 54.5% and for the untested cases was 22.0%. Compared to the entire provincial cohort (i.e. the gold standard) the 10-year (unadjusted) survival of the tested sub-cohort overestimated survival by 19.2%.

We repeated this analysis, but excluded women who had been tested two or more years from diagnosis (Fig. 2). In this analysis, the survival gap between the 902 tested women and the underlying population cohort narrowed considerably, but the gap was still substantial at ten years post-diagnosis (10.0%). The degree of over-estimation was greater if we included 1208 women tested within three years of diagnosis (15.4%) (Fig. 3). If we excluded all women tested after one or more years from diagnosis the gap narrowed to 4.1% at 10 years, but this exclusion criterion resulted in the inclusion of only 310 of the study subjects (21.8%).

The annual mortality rates for the entire cohort and for the tested cohort are presented in Table 1 and Fig. 4. The survival experiences of the tested cohort and the Ontario cohort, using the incidence density approach based on these rates, are constructed and compared to the entire cohort in Fig. 5. The survival of the tested cohort exceeded the survival of the provincial cohort by 6.1% at 10 years.

We then estimated the survival experience of the tested-cohort based on the left-truncated approach (9). The (adjusted) survival experience of the tested sub-cohort is compared with the unadjusted survival experience of the entire cohort in Fig. 6. The adjusted left-truncated analysis in SAS resulted in an overestimate of the provincial survival experience by 8.4% at 10 years – a small but substantial difference. The residual difference post-adjustment could be due either to methodologic limitations of the left-truncated survival analysis, or to a true underlying difference in the mortality rates of tested and untested women (i.e. over and above survivorship bias). To evaluate the robustness of the left-truncated survival analysis method as implemented in SAS, we constructed a simulated-tested cohort from the entire cohort (see Subjects and methods above). Using the simulated-tested data set, the left-adjusted survival analysis was able to reconstruct with accuracy the true underlying survival experience of the Ontario population (Figs 7). This comparison indicates that the statistical method is robust and that the better survivorship observed in the tested cohort, compared to the provincial average, is not a statistical artifact, but likely represents a true difference in mortality. We hypothesize that this better survival of the tested women is a result of symptomatic women preferentially excluding themselves from genetic testing. The annual mortality rates from ovarian cancer, by 1-year interval from time of diagnosis, for tested and all women are presented in Table 1 and Fig. 4. In the 3 years following diagnosis, the annual mortality rate for the tested women was less than that for untested women (15.1% vs 17.8%; p < 0.01), but the magnitude of the survival difference dissipated with time (Fig. 4). Over the entire
Table 1. Annual mortality rates for women with ovarian cancer

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<th>Year</th>
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<td>8</td>
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<tr>
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Fig. 4. Annual mortality among subjects, tested vs all Ontario.

Fig. 5. Survival of ovarian cancer among subjects, tested vs all Ontario, calculated by incidence density method.

discussion

In this study, we compare the 10-year survival rate of women with ovarian cancer who were tested for BRCA1 and BRCA2 mutations in a research setting with the survival of all ovarian cancer patients in the underlying population. We have found that tested patients have a superior survival than non-tested patients, and that the difference persists after adjustment for time to ascertainment. The annual mortality rate for the tested patients was 8.8% and for the entire population was 12.2%. Our results have implications for the interpretation of both the estimates of absolute survival and of relative survival. If survival rates are based on tested patients, all of whom are alive at the time of testing, then the survival experience will be overestimated, both for women who test positive for BRCA1 or BRCA2 mutations and for non-carriers. The magnitude of the overestimate can be extreme if there is a substantial lag between date of diagnosis and the date of testing and the data are not completely adjusted for ascertainment – in our study the mean lag was 23 months and the overestimate of 10-year survival was 19%.

In contrast, survival will not be over-estimated in a study if all eligible patients are tested, e.g. in a study where mutation status is based on paraffin-embedded tumor blocks. This was the strategy taken by Rennert et al. (10) for estimating survival after hereditary breast cancer and was the basis of the study of Boyd et al (11) for estimating survival from hereditary ovarian cancer. In the latter study, a total of 189 Jewish women with ovarian cancer were included, of whom 88 had a founder mutation. In that study, the BRCA-associated cancer patients experienced much better recurrence-free survival than non-carriers (p < 0.001) but the difference in actual survival was much smaller and the p-value was of borderline significance (HR = 0.79; 95% CI 0.63–1.00: p = 0.05). In this study, the median survival follow-up time was not given, but very few events (deaths or censored alive) were observed after 5 years.
and therefore differences in long-term survival could not be properly assessed. The studies of Rennert et al. and of Boyd et al. were feasible because the population was restricted to Jewish patients with and without founder mutations, because these can be assayed on paraffin-embedded tumor samples with relative ease.

In contrast, when studies are based on living patients, the potential for survivorship bias is appreciable. The survivorship bias is mitigated to an appreciable extent if adjusted rates are constructed. For example, Hyman et al. excluded patients who were tested two or more years after diagnosis and estimated the 10-year survival rate for BRCA1 carriers to be 20% and for BRCA2 carriers to be 70%. In our analysis, using this adjustment technique, the 10-year survival was overestimated by 10% – from 35.8% to 45.8%.

The other two methods of adjustment were more effective in reducing the extent of survivorship bias, but the bias was not eliminated. The data generated with a left-truncated survival analysis in SAS resulted in a 10-year survival rate that was 8.4% greater than the provincial average. This was the adjustment method employed by Bolton et al. In this study, 26 observational studies were pooled, which included 909 BRCA1 carriers, 304 BRCA2 carriers and 2666 non-carriers. It is notable that the carriers comprised 33% of the patient population, which is greatly in excess of the 13% that would be expected if carriers and non-carriers had been sampled in proportion to the underlying populations. Bolton et al. found the 5-year overall survival was 36% for non-carriers, 44% for BRCA1 carriers, and 52% for BRCA2 carriers. Not all the controls had undergone genetic testing. The study of Bolton et al. is impressive for the large number of subjects analyzed, but is less than ideal because of the large number of contributing centers (26), the over-representation of carriers, because not all control subjects had had a genetic test and because of the relatively short period of follow-up (5 years).

Out study did not compare women with and without mutations, that will be subject of another report. Rather, we studied the association between genetic testing per se and survivorship in a large cohort of women, all of whom were eligible for testing. We found that the mortality for the tested women was superior to that of the provincial cohort in the 3-year period following testing, but mortality rates were similar in years 4–12. The most straightforward explanation for this difference is that women who are ill or who have experienced a recurrence are less likely to have genetic testing than women who are in remission. If the difference in survival were due to an intrinsic difference in the aggressiveness of the cancers between tested and untested women, then we would expect the mortality difference to persist over the entire follow-up period. The data presented here imply that the impact of studying living tested patients is likely to overestimate the 10-year survival rates by approximately 10%, depending on the mean time lag from diagnosis to genetic testing. To minimize bias, the ideal study should compare carriers and non-carrier women who are derived from the same underlying population, either by testing paraffin-embedded tumor samples or by including only women who are tested shortly after diagnosis.

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References


BRCA1 and BRCA2 mutations in ovarian cancer