The incidence of pancreatic cancer in BRCA1 and BRCA2 mutation carriers

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BACKGROUND: Germline mutations in BRCA1 and BRCA2 predispose to pancreatic cancer. We estimated the incidence of pancreatic cancer in a cohort of female carriers of BRCA1 and BRCA2. We also estimated survival rates in pancreatic cancer cases from families with a BRCA mutation.

METHODS: We followed 5149 women with a mutation for new cases of pancreatic cancer. The standardised incidence ratios (SIR) for pancreatic cancer were calculated based on age group and country of residence. We also reviewed the pedigrees of 8140 pedigrees with a BRCA1 or a BRCA2 mutation for those with a case of pancreatic cancer. We recorded the year of diagnosis and the year of death for 351 identified cases.

RESULTS: Eight incident pancreatic cancer cases were identified among all mutation carriers. The SIR for BRCA1 carriers was 2.55 (95% CI = 1.03–5.31, P = 0.04) and for BRCA2 carriers was 2.13 (95% CI = 0.36–7.03, P = 0.3). The 5-year survival rate was 5% for cases from a BRCA1 family and 4% for cases from a BRCA2 family.

CONCLUSION: The risk of pancreatic cancer is approximately doubled in female BRCA carriers. The poor survival in familial pancreatic cancer underscores the need for novel anti-tumoural strategies.

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Germline mutations in various cancer susceptibility genes have been implicated in the pathogenesis of pancreatic cancer. These include BRCA1 and BRCA2 (Lal et al., 2000), TP53 (Caldas et al., 1994), PALB2 (Jones et al., 2009), p16/CDKN2A (Redston et al., 1994; Ghiorzio et al., 2012), SMAD4 (Hahn et al., 1996), STK 11 (Sato et al., 2001), ataxia-telangiectasia-mutated (ATM) gene (Roberts et al., 2011) and the mismatch repair genes (MMR) (Win et al., 2012). Familial pancreatic cancer accounts for about 5–10% of pancreatic cancers (Fernandez et al., 1994; Klein et al., 2001; Bartsch et al., 2004). In a study of 102 familial pancreatic cancer patients, Lal et al. (2000) identified five germline mutations; three mutations in BRCA2 gene and one mutation each in BRCA1 and p16.

Several other lines of evidence also suggest that carriers of BRCA1 or BRCA2 mutations face an increased risk of pancreatic cancer (Phelan et al., 1996; The Breast Cancer Linkage Consortium, 1999; Thompson et al., 2002; Risch et al., 2006). In the cross-sectional study of The Breast Cancer Linkage Consortium (1999), Thompson et al. (2002) reported a significant increase in the risk of pancreatic cancer in BRCA1 mutation carriers (RR = 2.26, 95% CI = 1.26–4.06, P = 0.004) and in BRCA2 mutation carriers (RR = 3.51, 95% CI = 1.87–6.58, P = 0.0012). In a study of 1171 unselected patients with ovarian cancer in Ontario, Risch et al. (2006) estimated the risk of pancreatic cancer among relatives of 977 proband patients with invasive ovarian cancer, including 127 with a BRCA1 or BRCA2 mutation. The relative risk for pancreatic cancer was 3.1 (95% CI = 0.43–21) in relatives of BRCA1 mutation carriers and 6.6 (95% CI = 1.9–23) in relatives of BRCA2 mutation carriers, compared with the relatives of non-carriers.
All previous studies are based on reviews of family histories and the diagnoses of pancreatic cancer relied on accurate information provided by a family member. Further, in previous studies, the mutation status of the pancreatic cancer cases was unknown. We have conducted the first prospective study of the incidence of pancreatic cancer in a cohort of BRCA1 and the BRCA2 mutation carriers. The knowledge of pancreatic cancer incidence rates has important implications for genetic counsellors and potentially for informing screening policies. We also estimated the survival rate of pancreatic cancer in cases from families with a known BRCA1 or BRCA2 mutation. Information on current survival rates may be obtained from GLOBOCAN 2008 (Ferlay et al., 2008) according to different countries and different age groups. The age-specific follow-up time in years. The person-years were subcategorised derived separately for carriers from each of five countries (Canada, British Columbia, and the United Kingdom). The 5149 carriers were included in this analysis were diagnosed before the date of genetic testing of the proband, but the specific years of diagnosis were not indicated. To estimate survival, patients were followed from the year of diagnosis to the years of death or the year the pedigree was constructed. The survival from the diagnosis was calculated by Kaplan–Meier method and the difference between groups was compared with the log-rank test of significance. We did not have information on the specific cause of death for the pancreatic cancer patients, and all deaths were assumed to be from pancreatic cancer.

RESULTS

Incidence

Five thousand eighty-nine women in our database of BRCA1 and BRCA2 carriers were followed for a mean of 1.95 years. We identified eight new pancreatic cancer cases among the BRCA1 carriers were followed for a mean of 1.95 years. We identified eight new pancreatic cancer cases among the BRCA1 and BRCA2 carriers vs 3.28 pancreatic cancers expected (SIR = 2.44, \( P = 0.03 \)). The characteristics of the eight incident cases are presented in Table 1. Six of the eight cases were confirmed by pathology report or medical record and two were based on the patient questionnaire. Of the eight pancreatic cancer cases, six cases occurred in BRCA1 carriers, vs 2.35 pancreatic cancers.

| Case no. | Mutation status | Pancreatic cancer, age of diagnosis | Previous breast cancer, age of diagnosis (years) | Smoking history | History of pancreatic cancer in first-degree relatives, age of diagnosis (years) |
|----------|----------------|----------------------------------|-----------------------------------------------|----------------|-----------------------------------------------|
| 1        | BRCA1          | 77                               | Yes, age 43                                   | No             | No                                            |
| 2        | BRCA2          | 59                               | No                                            | Yes            | No                                            |
| 3        | BRCA1          | 75                               | Yes, age 44                                   | No             | Yes, sister, age 79                           |
| 4        | BRCA1          | 67                               | Yes, age 60                                   | No             | No                                            |
| 5        | BRCA1          | 60                               | No                                            | Yes            | No                                            |
| 6        | BRCA1          | 65                               | No                                            | No             | No                                            |
| 7        | BRCA1          | 54                               | No                                            | Yes            | No                                            |
| 8        | BRCA1          | 53                               | No                                            | Yes, mother, age 77 | No                                            |
expected (SIR = 2.52, \( P = 0.04 \)) and two cases occurred in BRCA2 carriers vs 0.94 pancreatic cancers expected (SIR = 2.13, \( P = 0.3 \)) (Table 2). All eight pancreatic cancer cases were diagnosed in women aged 50 and above. For women above the age of 50, the annual incidence rate was 37 per 100 000 per year for BRCA1 carriers and 39 per 100 000 per year for BRCA2 carriers. The rates were estimated for women below and above age 65 in Table 3.

Interestingly, two of the incident case of pancreatic cancer had a first-degree relative with pancreatic cancer. Among the 5089 women in the follow-up study, 35 had a first-degree relative with pancreatic cancer. Among the 5089 cases from families with a BRCA1 mutation, 213 (3.7%) had a case of pancreatic cancer, and of 2269 families with a BRCA2 mutation, 138 (6.1%) had a case of pancreatic cancer. In aggregate, 317 cases were diagnosed in women below and above age 65 in Table 3.

Survival

Of 8140 families in the database, a total of 317 (3.9%) families had one or more individuals diagnosed with pancreatic cancer. Of 5742 families with a BRCA1 mutation, 213 (3.7%) had a case of pancreatic cancer, and of 2269 families with a BRCA2 mutation, 138 (6.1%) had a case of pancreatic cancer. In aggregate, 317 families included 351 subjects with pancreatic cancer (range 1–5). The mean age at diagnosis of pancreatic cancer was similar in cases from families with a BRCA1 and a BRCA2 mutation (BRCA1 = 63.4 years, range 20–90 years; BRCA2 = 62.7 years, range 27–90 years; \( P = 0.56 \)). Of the 351 cases of pancreatic cancer, 84% were diagnosed at age 50 or above (87% for BRCA1 carriers and 80% for BRCA2 carriers). Of the 351 cases of pancreatic cancer, 203 (58%) were in males and 148 (42%) were in females.

The mean survival from diagnosis to death was 1.07 years (range 0.5–6 years) for BRCA1 mutation carriers (SIR = 2.13). For BRCA2 mutation carriers (data not shown). The 5-year survival rate was 61% for cases with a BRCA1 mutation and 3.6% for cases with a BRCA2 mutation (Figure 1). We did not observe a significant survival difference between males and females among either the BRCA1 or BRCA2 mutation carriers (data not shown).

**DISCUSSION**

In the prospective component of this study of BRCA1 and the BRCA2 mutation carriers, we saw a statistically significant 2.4-fold increase in the incidence of pancreatic cancer in female BRCA mutation carriers (\( P = 0.03 \)). The increase in the incidence of pancreatic cancer was similar for BRCA1 mutation carriers (SIR = 2.55) and BRCA2 mutation carriers (SIR = 2.13). For women above the age of 50, the annual risk of pancreatic cancer for a woman with a mutation in either gene was 0.04%. In this prospective study, we do not have data on males with either
mutation. However, based on the sex distribution of pancreatic cases in our pedigree review (203 males: 148 females), we expect the risk of pancreatic cancer to be slightly higher in males.

In our study, the absolute risks of pancreatic cancer were similar for BRCA1 and BRCA2 carriers; in other studies, the risks for BRCA2 carriers exceeded that for BRCA1 carriers. In particular, the Breast Cancer Linkage Consortium (BCLC) reported a 2.2-fold increase in the risk of pancreatic cancer among BRCA1 mutation carriers ($P = 0.004$) (Thompson et al., 2002) and a 3.5-fold increase in the risk of pancreatic cancer was reported in the BRCA2 carriers ($P = 0.0012$) (The Breast Cancer Linkage Consortium, 1999).

We measured survival in the pancreatic patients recorded in the pedigrees for the families in the data set. We did not have the mutation status of the cancers observed in relatives and a proportion of these will likely not carry the familial BRCA mutation. We observed a poor overall survival in both men and women with a BRCA1 mutation or a BRCA2 mutation. The average time from diagnosis to death was ~1 year for both groups and the 5-year survival was 5% for BRCA1 carriers and 4% for BRCA2 carriers. The poor survival in our cohort is similar to that of the general population, where the 5-year survival is 6% (Canadian Cancer Society, 2010).

Our study has a number of limitations pertaining to both the estimation of the incidence and overall survival. Our cohort study includes only women and therefore we cannot estimate the incidence of pancreatic cancer in males. The number of incidence cases was relatively small (eight) and this limits the precision of the risk estimates, especially for subgroups. To record overall survival, we obtained the age of diagnosis and death on the patients with pancreatic cancer from the review of family pedigrees based on the probands interview. Moreover, it was not possible to review the pathology reports to confirm the diagnosis in the relatives. Some patients may have died of causes other than the pancreatic cancer, but this number is likely to be small.

Our study has implications for the planning of a screening programme for pancreatic cancer in men and women with a BRCA1 or BRCA2 mutation. The estimated annual incidence rate for women over the age of 50 was 0.04% for BRCA1 and BRCA2 carriers, and the results of our study do not support the adoption of a screening policy (if we were to screen 1000 carriers annually for 10 years, we would expect to detect approximately four pancreatic cancers).

Among women with a mutation and a first-degree relative with pancreatic cancer the risk was much higher (annual risk = 1.0%). The high relative risk for women with a family history was based on only two incident cases (one with a mutation in BRCA1 and one in BRCA2) and the confidence limits are wide. However, this observation suggests that there may be modifying genes associated with the development of pancreatic cancer in these families. Furthermore, it has not yet been shown that screening for pancreatic cancer is associated with a reduction in mortality from the disease and screening should not be recommended outside of clinical trials.

The poor survival observed among pancreatic cancer patients in these families does not appear to be different from that of patients in the general population and emphasises the need for better prevention strategies and novel chemotherapies. It is possible that some drugs (e.g., cisplatinum) might potentially benefit specifically BRCA1 and BRCA2 carriers diagnosed with pancreatic cancer (van der Heijden et al., 2005; Lowery et al., 2011) and clinical trials are indicated.

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APPENDIX

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