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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* mutation. 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; Ghiorzo *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 = 0.45–21) 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.

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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 relevant before initiating therapies for women or men with a *BRCA1* or *BRCA2* mutation.

MATERIALS AND METHODS

Incidence

We estimated the incidence of pancreatic cancer in a cohort 5149 women with a known *BRCA1* or *BRCA2* mutation in women who completed a baseline questionnaire and who had completed at least one follow-up questionnaire. The cohort was assembled from 50 study centres in 10 different countries. The 5149 carriers were from 3878 different families. Each woman was proven to be a carrier of a deleterious mutation in *BRCA1* or *BRCA2* by direct DNA sequencing. Women with a past history of breast cancer or of skin cancer were eligible for the study but women with a past history of ovarian cancer or of another cancer were excluded. All women had completed a risk questionnaire at study entry and a follow-up questionnaire every 2 years thereafter. The baseline and follow-up questionnaires were standardised across the study centres. Women were followed from the date at the baseline until the date of last questionnaire, the diagnosis of pancreatic cancer, diagnosis of ovarian cancer or death from another cause. Of 5149 women, 60 women had data missing on key variables (e.g., date of birth, date of questionnaires, gene mutation) and were excluded, leaving 5089 women in final analysis. The diagnosis of pancreatic cancer was confirmed by reference to a pathology report or medical record where possible.

The risk of pancreatic cancer in the *BRCA1* and *BRCA2* mutation carriers, relative to the general population, was estimated with standardised incidence ratios (SIRs). The SIR was obtained by calculating the ratio of observed to expected number of new pancreatic cancer cases, for all women combined and then separately for *BRCA1* and the *BRCA2* carriers. To do so, the observed and expected numbers of pancreatic cancers were derived separately for carriers from each of five countries (Canada, United States, Poland, France and Italy). First, the annual age-standardised incidence rates of pancreatic cancer were calculated with the count (numerator) and person-year at risk (denominator). The person-years at risk were calculated using the total number of *BRCA1* and *BRCA2* carriers multiplied with the average follow-up time in years. The person-years were subcategorised according to different countries and different age groups. The age-standardised incidence rates for each participating country were obtained from GLOBOCAN 2008 (Ferlay *et al*, 2010). The expected number of pancreatic cancers was calculated by multiplying each age-standardised incidence rate of the country-specific general population by the observed person-years in our *BRCA* cohort and divided by 100 000 to get the expected numbers of pancreatic cancers (indirect standardisation method). The SIRs were also estimated for age subgroups <65 years and $\geqslant 65$ years. We divided the cohort of women into those with and without a first-degree relative with pancreatic cancer and into those who did and who did not develop pancreatic cancer during the follow-up period. We then estimated the univariate odds ratio for the development of pancreatic cancer, conditional on the presence of a first-degree relative affected with pancreatic cancer, based on the two by two table.

Overall survival

In a separate analysis, we reviewed the pedigrees of all families in the database with a *BRCA1* or a *BRCA2* mutation. This included 8140 pedigrees from families with a known *BRCA1* or *BRCA2* mutation, enrolled at one of 50 centres across North America and Europe. Families were ascertained on the basis of breast and ovarian cancers (but not pancreatic cancer); we then identified families with one or more individuals with pancreatic cancer. The pancreatic cancer subjects were included if they were a first-, second- or third-degree relative of a known carrier. A total of 351 pancreatic cancers were identified. Of these, 163 were in first-degree relatives of a known carrier, 143 were in second-degree relatives and 45 were in third-degree relatives. We recorded the age at diagnosis and age at death for each case, from the information provided on the pedigree diagram, where available. We did not have the mutation status of these patients and the diagnosis was based on information provided by the proband at interview, when the pedigree was constructed. All cases of pancreatic cancer that 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* 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

Table 1 Characteristics of the incident cases of pancreatic cancer in the *BRCA* cohort.

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	*BRCA2*	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	No	Yes, mother, age 77

Table 2 Observed and expected numbers of pancreatic cancers in *BRCA1* and *BRCA2* carriers according to the major contributing country

Country	BRCA status	*N*	Person-years	Expected cancers	Observed cancers	SIR 95% CI	*P*-value (two-tailed)
Canada	All	1493	8801.07	1.21	2	1.65 (0.28–5.45)	0.4
	BRCA1	846	5058.73	0.65	1	1.54 (0.07–7.63)	0.6
	BRCA2	647	3742.34	0.57	1	1.76 (0.09–8.69)	0.5
USA	All	1437	7639.41	1.15	2	1.73 (0.29–5.72)	0.4
	BRCA1	973	5373.37	0.80	1	1.25 (0.06–6.18)	0.7
	BRCA2	464	2266.04	0.35	1	2.80 (0.14–13.82)	0.3
Poland	All	2020	9312.29	0.84	2	2.36 (0.39–7.81)	0.3
	BRCA1	2013	9292.51	0.84	2	2.37 (0.39–7.84)	0.2
	BRCA2	7	19.78	0.003	0	—	—
France	All	64	348.30	0.04	1	25 (1.25–123.3)	0.04
	BRCA1	51	273.18	0.03	1	33.3 (1.66–164.4)	0.03
	BRCA2	13	75.12	0.01	0	-	—
Italy	All	75	371.83	0.04	1	25 (1.25–123.3)	0.04
	BRCA1	59	283.43	0.03	1	33.3 (1.66–164.4)	0.03
	BRCA2	16	88.40	0.01	0	—	—
All countries	All	5089	26 472.90	3.28	8	2.44 (1.13–4.63)	0.03
	BRCA1	3942	20 281.23	2.35	6	2.55 (1.03–5.31)	0.04
	BRCA2	1147	6191.67	0.94	2	2.13 (0.36–7.03)	0.3

Abbreviations: CI = confidence interval; SIR = standardised incidence ratio.

Table 3 Observed and expected numbers of pancreatic cancers in *BRCA1* and *BRCA2* carriers by age groups

Age (years)	*N*	Person-years	Expected cancers	Observed cancers	SIR 95% CI	*P*-value (two-tailed)
All						
<65	4532	22 996.66	1.68	3	1.79 (0.45–4.86)	0.3
⩾65	557	3476.23	1.61	5	3.10 (1.14–6.88)	0.03
BRCA1						
<65	3566	17 931.4	1.25	2	1.6 (0.26–5.29)	0.4
⩾65	376	2349.82	1.09	4	3.67 (1.16–8.85)	0.03
BRCA2						
<65	966	5065.26	0.43	1	2.33 (0.12–11.47)	0.4
⩾65	181	1126.41	0.52	1	1.92 (0.09–9.48)	0.5

Abbreviations: CI = confidence interval; SIR = standardised incidence ratio.

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 are 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 (data for 615 women was missing). The odds ratio for developing pancreatic cancer for those with a first-degree relative was 46.5 (95% CI = 9.4–230, $P < 0.0001$), compared with women without a first-degree relative.

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 and 1.00 years (range 0.5–6 years) for *BRCA2* mutation carriers ($P = 0.83$). The 5-year survival rate was 6.1% 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

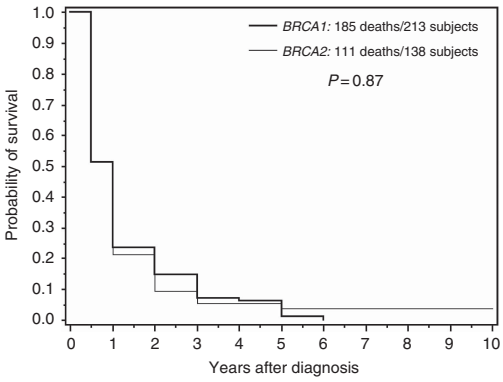

Figure 1 Survival after pancreas cancer by BRCA mutation.

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

Other members of the Hereditary Breast Cancer Clinical Study Group: Ophira Ginsburg, André Robidoux, Louise Maehle, Kevin Sweet, Dawna Gilchrist, Olufunmilayo I. Olopade, Fergus Couch, Claudine Isaacs, Beth Karlan, Charis Eng, Jeffrey N. Weitzel, Mary B. Daly, Judy E. Garber, Dana Zakalik, Carey A. Cullinane, Dominique Stoppa-Lyonnet, Howard Saal, Wendy Meschino, Wendy McKinnon, Marie Wood, Taya Fallen, Raluca Kurz, Siranoush Manoukian, Barry Rosen, Rochelle Demsky, Edmond Lemire, Jane Mclennan, Seema Panchal, Albert E. Chudley, Susan T. Vadaparampil, Tuya Pal, Daniel Rayson, Adriana Valentini, Susan Friedman (on behalf of FORCE) Cezary Cybulski, Jacek Gronwald, Tomasz Byrski, Tomasz Huzarski.