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Research Article

Risk of Pancreatic Cancer in Breast Cancer Families from the Breast Cancer Family Registry

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Abstract

Background: Increased risk of pancreatic cancer has been reported in breast cancer families carrying *BRCA1*and *BRCA2* mutations; however, pancreatic cancer risk in mutation-negative (BRCAX) families has not been explored to date. The aim of this study was to estimate pancreatic cancer risk in high-risk breast cancer families according to the BRCA mutation status.

Methods: A retrospective cohort analysis was applied to estimate standardized incidence ratios (SIR) for pancreatic cancer. A total of 5,799 families with ≥1 breast cancer case tested for mutations in *BRCA1* and/or *BRCA2* were eligible. Families were divided into four classes: BRCA1, BRCA2, BRCAX with ≥2 breast cancer diagnosed before age 50 (class 3), and the remaining BRCAX families (class 4).

Results: *BRCA1* mutation carriers were at increased risk of pancreatic cancer [SIR = 4.11; 95% confidence interval (CI), 2.94–5.76] as were *BRCA2* mutation carriers (SIR = 5.79; 95% CI, 4.28–7.84). BRCAX family members were also at increased pancreatic cancer risk, which did not appear to vary by number of members with early-onset breast cancer (SIR = 1.31; 95% CI, 1.06–1.63 for class 3 and SIR = 1.30; 95% CI, 1.13–1.49 for class 4).

Conclusions: Germline mutations in *BRCA1 and BRCA2* are associated with an increased risk of pancreatic cancer. Members of BRCAX families are also at increased risk of pancreatic cancer, pointing to the existence of other genetic factors that increase the risk of both pancreatic cancer and breast cancer.

Impact: This study clarifies the relationship between familial breast cancer and pancreatic cancer. Given its high mortality, pancreatic cancer should be included in risk assessment in familial breast cancer counseling.
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Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the United States and leads to an estimated 227,000 deaths per year worldwide (1). The majority of pancreatic cancers are sporadic with a median age at diagnosis of 72 years; the male:female ratio is 1.3:1, and cigarette smoking accounts for approximately 20% of tumors (2). It has been estimated that approximately 7% to 10% of patients with pancreatic cancer have one or more close relatives with pancreatic cancer (3) and are therefore classified as having familial pancreatic cancer (FPC). Relatives of FPC cases are at increased risk of developing pancreatic cancer compared with the general population, and the risk increases with an increasing number of affected relatives and younger age at diagnosis (4, 5).

It is still unknown what genetic factors cause most familial clustering of pancreatic cancer. About 6% to 17% of FPC cases are found to carry germline mutations in *BRCA2* (6–8), approximately 3% have *PALB2* mutations (9–11) and 2% carry deleterious *ATM* mutations (12). Almost all FPC cases with germline *PALB2* mutations have at least one close relative with breast cancer.

BRCA1, BRCA2, and *PALB2* form a trimeric complex, which is critical for the maintenance of genomic stability by repairing DNA damage (13). The same genes, in particular *BRCA1* and *BRCA2*, are also found to be

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mutated in a high percentage of families with hereditary breast and ovarian cancer. Members of these families are at an increased risk of developing pancreatic cancer compared with the general population, that has been estimated to be 2- to 7-fold (14–17) for *BRCA2* mutation carriers and 2-fold for *BRCA1* mutation carriers (17, 18).

On the basis of these previous reports, the goal of the present study was to estimate the relative risk of pancreatic cancer in a large series of families recruited by the Breast Cancer Family Registry (BCFR) according to their *BRCA1* and *BRCA2* mutation status. It also aimed to assess, for the first time, the risk of pancreatic cancer among relatives of individuals who test negative for mutations in these genes.

Materials and Methods

Selection and description of families

The BCFR is an international consortium enrolling and studying high-risk breast cancer families from 6 centers in the United States (Northern California Breast Cancer Family Registry, New York site of the BCFR, Utah site of BCFR, Philadelphia site of the BCFR), Canada (Ontario Familial Breast Cancer Family Registry), and Australia (Australian Breast Cancer Family Registry). The BCFR collects cancer family history, epidemiologic data, and histopathologic data on individuals affected with breast cancer, ascertained through population-based cancer registries (population-based breast cancer families) or family cancer clinics and community outreach (clinic-based breast cancer families; ref. 19). For the present study, families were eligible if the proband (defined in this context as the first family member enrolled in the BCFR and affected with breast cancer) had been screened for pathogenic mutations in *BRCA1* and/or *BRCA2*. According to the mutational status of the proband, families were classified as BRCA1, BRCA2, and BRCAX (proband tested negative for mutations in both genes). BRCAX families were subdivided in 2 classes: those with at least 2 early onset ($\leq$50 years) breast cancer cases (class 3) and those remaining (class 4). Seven families segregating both *BRCA1* and *BRCA2* mutations were excluded.

Mutation analysis testing

Details on the definition of deleterious *BRCA1* and *BRCA2* mutations and the techniques used to detect them are provided in the Supplementary Methods.

Data collection

For all included individuals, information on diagnoses of breast, ovarian, and pancreatic cancers, ages at diagnosis of these cancers, date of birth and last contact or death was collected by personal or telephone interview or by mailed questionnaire. The proband in each family provided information on cancer family history through a family history questionnaire. Overall, documented verification through pathology reports (cancer registries and medical records) was available for 63% of breast cancers (20).

Age at diagnosis of pancreatic cancer was imputed as age at death for 34 cases and as the difference between date of birth and date of last contact for 5 cases. Subjects for which no age was recorded at any event (interview, cancer diagnosis, death, or last follow-up) were excluded.

Statistical analysis

To test whether there was any difference in age at diagnosis of pancreatic cancer among the 4 classes of families we applied one-way ANOVA. To estimate the relative risk of pancreatic cancer for individuals from the 4 groups of families, we applied a survival analysis considering the time in years from birth to diagnosis of pancreatic cancer, death, or last contact.

In total, there were 78,820 individuals included from 5,799 eligible families: 12,180 women and 157 men with breast cancer, 1,257 women with ovarian cancer, and 417 individuals with pancreatic cancer (219 men and 198 women). Of the 11,946 individuals in 538 BRCA1 families, 1,094 were genotyped mutation carriers (500 unaffected and 593 affected with breast or ovarian cancer, one affected with pancreatic cancer) and 717 we genotyped noncarriers (655 unaffected, 62 affected). There were 7,773 individuals in 383 BRCA2 families, of which 781 determined to be mutation carriers (360 unaffected and 420 affected with breast or ovarian cancer, one affected with pancreatic cancer) and 523 genotyped noncarriers (479 unaffected, 44 affected).

We estimated the relative risk of pancreatic cancer as a standardized incidence ratio (SIR), defined as the number of pancreatic cancer cases observed divided by the number expected on the basis of incidence rates for the general population. The expected number of cases was calculated by multiplying person-years at risk with population incidence rates of pancreatic cancer. Person-time, SIRs, and their 95% confidence intervals (CI) were calculated using the *stptime* command in STATA version 10 (Stata Corporation). Population incidence rates specific to country, sex, and 5-year age group for specific 10-year calendar periods were taken from Cancer Incidence in Five Continents Reports (IARC-WHO; update November 2010).

To assess the possible influence of cohort effects, we first based the analysis on decade-specific incidence rates. For this analysis, follow-up began in 1950 because no reliable estimates of pancreas rates are available before then. Once we verified that the SIR estimates were not influenced by such cohort-effects, our final analyses were based on population rates specific for each country, sex, and 5-year age group averaged from 1950 to 2009 which were applied to all follow-up, regardless of calendar year. Members of each class of family were first analyzed for overall pancreatic cancer risk. We then conducted separate analyses stratified by gender, age ($\leq$50 vs. > 50 years), degree of relationship to the proband [first-degree relative (FDR)], method of family recruitment (clinic-based vs. population-based) and, for BRCA1 and BRCA2 families, the number of breast cancer cases in the family ($\leq$2 vs. $\geq$3 breast cancer cases).

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Because relatively few family members were tested for mutations in *BRCA1* or *BRCA2*, we conducted the analyses using 2 different approaches. First, we categorized all family members according to the mutational status of the proband. Under the second approach, we weighted individuals from BRCA1 and BRCA2 families according to their estimated probability of being a mutation carrier. These probabilities were estimated using the SLINK software (http://linkage.rockefeller.edu/soft/slink.html). SLINK's algorithm (21) simulates genotypes conditional on any combination of phenotypes and genetic marker data, even if only partially available. If N is the total number of members of a family, x ($x_1, x_2, \ldots, x_N$) is the vector of their phenotypes, and $g = (g_1, g_2, \ldots, g_N)$ the vector of genotypes to be imputed, then the conditional probability distribution of the genotypes given the phenotypes can be calculated by a series of successive calculations:

$$P(g|x) = P(g_1|x)\, P(g_2|g_1, x) P(g_3|g_1, g_2, x) \ldots$$

BRCA1 and *BRCA2* mutation status was imputed for all family members using personal history of breast, ovarian, and pancreas cancer as phenotypic data and mutation status, if tested, as genetic data. Age-specific breast, ovarian, and pancreas cancer penetrance and incidence estimates for *BRCA1* and *BRCA2* mutation carriers were also included as liability classes. The liability classes were constructed with 7 age brackets for each of the following groups of individuals: affected with breast cancer, affected with ovarian cancer, and unaffected with breast cancer or ovarian cancer. These classes reflected the penetrance and incidence estimates derived from a combined analysis of 22 data sets unselected for family history by Antoniou and colleagues (ref. 22; Supplementary Table S1). For pancreatic cancer, we included an additional liability class with an assumed incidence in noncarriers of 0.005 and a risk in carriers that was initially set to that for noncarriers and then iterated as 0.005 multiplied by the current estimate of the SIR. Genotype simulation conditional on the pedigree phenotypes, relationships, and observed genotypes was conducted 2,000 times for the entire BRCA1 and BRCA2 set of families.

For each individual included in this analysis, the probability of being a mutation carrier was estimated as the proportion of simulations in which they were imputed to be mutation carriers. This probability was then used as a weight in the estimation of the SIR. This process was repeated until the SIR for pancreatic cancer for *BRCA1* and *BRCA2* mutation carriers converged, defined in this case to be a change from the previous iteration in the SIR of <0.5%.

To compare SIRs obtained in stratified analyses, we estimated P values by applying a rate parameter test (23).

Results

Description of families

Table 1 summarizes the characteristics of the families included in the study. There were 538 families for which the proband tested positive for a pathogenic mutation in *BRCA1*. Of these, 61 (11.3%) had at least one relative affected with pancreatic cancer and 4 (0.7%) had 2 or more affected relatives. There were 383 families found to carry *BRCA2* mutations; 49 (12.8%) had at least one relative diagnosed with pancreatic cancer and 7 (1.8%) had 2 or more. Of the BRCAX families, 1,219 had at least 2 relatives with early onset ($\leq$ 50 years) breast cancer (class 3); 71 (5.8%) reported at least one relative affected with pancreatic cancer and 10 (0.8%) had 2 or more. Among the 3,659 other BRCAX (class 4) families, 186 (5.1%) included at least one individual diagnosed with pancreatic cancer and 16 (0.4%) included 2 or more.

Table 1. Classes of families and characteristic of pancreatic cancer–affected members of BCFR

Class	BRCA1	BRCA2	3 (BRCAX)	4 (BRCAX)
Selection criteria	Proband carrier of a *BRCA1* mutation	Proband carrier of a *BRCA2* mutation	Proband tested negative for *BRCA1* and *BRCA2* mutations; 2 or more BC < = 50 years	Proband tested negative for *BRCA1* and *BRCA2* mutations; at least 1 BC
No. of families	538	383	1,219	3,659
No of individuals (men/women)	11,946 (5,457/6,490)	7,773 (3,502/4,271)	17,037 (7,158/9,879)	42,064 (18,461/23,603)
No. of PC cases	67 57 families: 1 PC 4 families: $\geq$2 PC	62 42 families: 1 PC 7 families: $\geq$2PC	82 61 families: 1 PC 10 families: $\geq$2PC	206 170 families: 1 PC 16 families: $\geq$2PC
Gender (PC cases only)	32 males 35 females	35 males 27 females	40 males 42 females	112 males 94 females
Mean age at diagnosis of PC	65.9 y (14.9)	63.1 y (11.0)	66.9 y (12.7)	66.9 y (12.5)

Abbreviations: BC, breast cancer; PC, pancreatic cancer.

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The percentage of men and women among pancreatic cancer cases was similar in all classes of families, with a slightly higher number of affected men, except in class 3 families which showed a higher number of women with pancreatic cancer. The observed mean age at diagnosis of pancreatic cancer was lower for BRCA2 families (63.1 years) than for the other 3 classes of families (>65.9), but this difference was not statistically significant (P = 0.22; Table 1).

Pancreatic cancer risk estimates by family class regardless of mutation carrier status

The estimated SIRs for pancreatic cancer by familial class are summarized in Table 2. Overall, the SIR for members of *BRCA1* mutation carrier families was 1.60 (95% CI, 1.26–2.04) and was similar for men (SIR = 1.43; 95% CI, 1.01–2.03) and women (SIR = 1.80; 95% CI, 1.29–2.51). The SIR was higher for family members aged ≤50 years than for older ones (4.68; 95% CI, 2.66–8.25 vs. 1.40; 95% CI, 1.08–1.83, $P = 0.00092$). The SIR did not appear to differ by the number of relatives with breast cancer (≤2 vs. ≥3 breast cancer, $P = 0.16$), nor by the family recruitment method (clinic-based vs. population-based, $P = 0.38$).

Overall, pancreatic cancer risk among members of BRCA2 families was 2.20-fold higher (95% CI, 1.71–2.82) than in the general population with no difference between men and women. The SIR was higher for younger than for older individuals (SIR = 4.77; 95% CI, 2.39–9.55 vs. SIR = 2.03; 95% CI, 1.56–2.66, $P = 0.043$). The family recruitment method did not appear to influence the relative risk of pancreatic cancer for members of BRCA2 families ($P = 0.67$). Having fewer relatives with breast cancer appeared to be associated with a greater risk (P = 0.0013).

Individuals from BRCAX class 3 families had an increased risk of developing pancreatic cancer compared with the general population (SIR = 1.31; 95% CI, 1.06–1.63) and this relative increase was similar for men and women. The estimated SIR was higher for younger relatives (SIR = 2.26; 95% CI, 1.17–4.34 vs. SIR = 1.24; 95% CI, 0.99–1.57) and for families recruited by clinics (SIR = 1.57; 95% CI, 1.20–2.06 vs. SIR = 1.02; 95% CI, 0.71–1.46 for population-based families), but these differences were not statistically significant ($P = 0.12$ and 0.056, respectively).

Overall, the SIR for members of class 4 families was 1.30 (95% CI; 1.13–1.49) and this did not differ by gender. The SIR was higher for younger family members than for older ones (SIR = 2.32; 95% CI, 1.54–3.49 vs. SIR = 1.23; 95% CI, 1.07–1.42, respectively, $P = 0.0085$). The estimated SIR was also higher for members of clinic-based families than for population-based families, but the difference was not statistically significant (SIR = 1.49; 95% CI, 1.21–1.82 vs. SIR = 1.18; 95% CI, 0.98–1.42, $P = 0.098$).

Pancreatic cancer risk for *BRCA1* and *BRCA2* mutation carriers: results using imputed genotypes

Estimated SIRs for *BRCA1* and *BRCA2* mutation carriers are summarized in Table 3. On the basis of a weighted analysis as a function of the imputed probability of being a mutation carrier, *BRCA1* mutation carriers were estimated to be at increased risk of pancreatic cancer (SIR = 4.11; 95% CI, 2.94–5.76), with little evidence of a difference by gender ($P = 0.090$). In the analysis stratified by age group, the SIR estimate was greater for individuals aged <50 years (7.75; 95% CI, 3.38–17.7) than for those who were older (SIR = 3.77; 95% CI, 2.61–5.44); however, the difference between the 2 groups was not statistically significant ($P = 0.15$).

BRCA2 mutation carriers were also found to be at increased risk of pancreatic cancer compared with the general population (SIR = 5.79; 95% CI, 4.28–7.84). Results were similar for men and women. *BRCA2* mutation carriers ≤50 years had a higher SIR (9.90; 95% CI, 4.28–22.9) for pancreatic cancer than for older ones (SIR = 5.45; 95%

Table 2. Estimated SIRs and CIs for pancreatic cancer by class of family from the BCFR

	BRCA1			BRCA2			3 (BRCAX)			4 (BRCAX)		
Class	**Obs**	**Exp**	**SIR (95% CI)**	**Obs**	**Exp**	**SIR (95% CI)**	**Obs**	**Exp**	**SIR (95% CI)**	**Obs**	**Exp**	**SIR (95% CI)**
Overall	67	41.8	1.60 (1.26–2.04)	62	28.2	2.20 (1.71–2.82)	82	62.6	1.31 (1.06–1.63)	206	158	1.30 (1.13–1.49)
Men	32	22.3	1.43 (1.01–2.03)	35	14.7	2.38 (1.71–3.31)	40	31.2	1.28 (0.94–1.75)	112	77.6	1.44 (1.20–1.74)
Women	35	19.4	1.80 (1.29–2.51)	27	13.5	2.00 (1.37–2.91)	42	31.4	1.34 (0.99–1.81)	94	80.8	1.16 (0.95–1.42)
≤50 y	12	2.56	4.68 (2.66–8.24)	8	1.67	4.77 (2.39–9.54)	9	3.99	2.26 (1.17–4.34)	23	9.92	2.32 (1.54–3.49)
>50 y	55	39.2	1.40 (1.08–1.83)	54	26.6	2.03 (1.56–2.66)	73	58.6	1.25 (0.99–1.57)	183	148	1.23 (1.07–1.42)
FDRs	13	5.91	2.20 (1.28–3.79)	16	5.42	2.95 (1.81–4.81)	22	19.0	1.16 (0.76–1.76)	83	67.0	1.24 (1.00–1.54)
Population-based	16	8.15	1.96 (1.20–3.20)	16	6.71	2.38 (1.46–3.89)	30	29.4	1.02 (0.71–1.46)	112	95.1	1.18 (0.98–1.42)
Clinic-based	51	33.6	1.52 (1.15–2.00)	46	21.5	2.14 (1.60–2.85)	52	33.1	1.57 (1.20–2.06)	94	63.2	1.49 (1.21–1.82)
≤2 BC	28	14.0	2.00 (1.38–2.89)	34	9.84	3.45 (2.47–4.83)						
≥3 BC	39	27.7	1.41 (1.03–1.92)	28	18.4	1.52 (1.05–2.21)						

Abbreviations: BC, breast cancer; Exp, expected number of cases; Obs, observed number of cases.

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Table 3. Estimated pancreatic cancer SIRs for *BRCA1* and *BRCA2* mutation carriers from the BCFR

	BRCA1 mutation carriers			BRCA2 mutation carriers		
	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)
Overall	34.0	8.26	4.11 (2.94—5.76)	41.8	7.23	5.79 (4.28–7.84)
Men	14.8	4.79	3.09 (1.86–5.15)	22.5	3.88	5.81 (3.84–8.78)
Women	19.2	3.47	5.52 (3.53–8.64)	19.3	3.35	5.77 (3.69–9.01)
≤50 y	5.59	0.72	7.75 (3.38–17.7)	5.47	0.55	9.90 (4.28–22.9)
>50 y	28.4	7.54	3.77 (2.61–5.44)	36.4	6.68	5.45 (3.94–7.54)
FDRs	11.2	2.51	4.47 (2.49–8.03)	13.6	2.45	5.55 (3.27–9.45)
Population-based	5.88	2.19	2.68 (1.20–6.02)	11.5	2.25	5.12 (2.88–9.12)
Clinic-based	28.1	6.07	4.63 (3.20–6.70)	30.3	4.98	6.09 (4.27–8.70)
≤2 BCs	13.8	3.31	4.18 (2.47–7.08)	24.2	2.70	8.98 (6.03–13.4)
≥3 BCs	20.1	4.95	4.07 (2.63–6.30)	17.6	4.52	3.90 (2.44–6.21)

Abbreviations: BC, breast cancer; Exp, expected number of cases; Obs, observed number of cases.

CI, 3.94–7.54), but the difference was not statistically significant ($P = 0.22$). Having fewer relatives with breast cancer appeared to be associated with a greater relative risk of pancreas cancer ($P = 0.0073$). Figure 1 compares the SIR estimates and 95% CIs for pancreatic cancer between *BRCA1* and *BRCA2* mutation carriers and BRCA1 and BRCA2 families.

Discussion

This study confirms previous reports that *BRCA2* mutation carriers have an increased risk of developing pancreatic cancer compared with the general population. It also supports previous evidence that *BRCA1* mutation carriers have increased pancreatic cancer risk, but with a higher relative risk than that estimated by other studies. Furthermore, the availability of a large number of high-risk pancreatic cancer families negative for *BRCA1 and BRCA2* mutations (~5,200) has provided a unique opportunity to estimate pancreatic cancer risk in non-mutation carriers from families with breast and ovarian cancer.

The association between *BRCA2* mutations and pancreatic cancer risk has been previously investigated; individuals from *BRCA2* mutation carrier families have been reported to have a pancreatic cancer risk ranging from 2- to 7-fold higher than general population (14,16,17,24). In our study, we observed a relative risk of 5.79 (95% CI, 4.28–7.84), slightly higher than most previous estimates. Unlike previous studies, which were mostly limited to FDRs of the index case, we also considered more distant relatives (up to third-degree); however, our result was consistent for FDRs (SIR = 5.55; 95% CI, 3.27–9.45). Previous reports on *BRCA2* mutation carriers aged <65 years showed from 5- to 37-fold increased risk of pancreatic cancer (14, 15). We applied a more extreme phenotype as early onset pancreatic cancer (≤50 years) and estimated a 9.90-fold higher risk than the general population (95% CI, 4.28–22.9). We also observed in *BRCA2* mutation carrier families a mean age at pancreatic cancer diagnosis of 63.1 years, approximately 9 years earlier than the mean age of pancreatic cancer in the general population (1).

Data from previous studies on the role of germline *BRCA1* mutations in pancreatic cancer carcinogenesis are more controversial than those for *BRCA2* mutations; some studies reported 2-to 3-fold higher risk of pancreatic cancer in *BRCA1* mutation carriers than in the general population (18, 24). A recently published study reported that Ashkenazi Jewish families with aggregation of breast cancer and pancreatic cancer had a similar percentage of *BRCA1* and *BRCA2* mutations (25). We also observed a similar percentage of families with *BRCA1* and *BRCA2* mutations and aggregation of breast cancer and pancreatic cancer (Table 1). Our study, the largest to date assessing pancreatic cancer risk in *BRCA1* carriers, estimated a 4.11-fold higher risk of pancreatic cancer, which is higher than estimates from previous reports. The SIR was 4.47 for FDRs of the proband. A previous study estimated that *BRCA1* mutation carriers have >3-fold risk of pancreatic cancer at ages less than 65 years (18); we estimated an SIR of 7.75 (95% CI, 3.38–17.7) for individuals aged less than 50 years. In addition, the mean age at diagnosis of pancreatic cancer in members of *BRCA1* mutation carrier families was 65.9 years, which is 6 years earlier than the mean age at pancreatic cancer diagnosis in the general population (1). The above-reported relative risks of pancreatic cancer for *BRCA1* and *BRCA2* mutation carriers were estimated using imputed carrier probabilities for untested family members (Table 3). The same individuals were analyzed for pancreatic cancer risk, regardless of their mutation status (Table 2), with lower SIR estimated both for the overall and all stratified analyses (Fig. 1).

A recent study prospectively followed more than 5,000 female carriers of mutations in *BRCA1* and *BRCA2* for a mean time of 1.95 years. On the basis of 6 incident pancreatic cancers in *BRCA1* mutation carriers and 2 *BRCA2* mutation carriers, they estimated SIRs of 2.55 (95% CI, 1.03–5.31) and 2.13 (95% CI, 0.36–7.03), respectively; furthermore, they estimated an increased risk of

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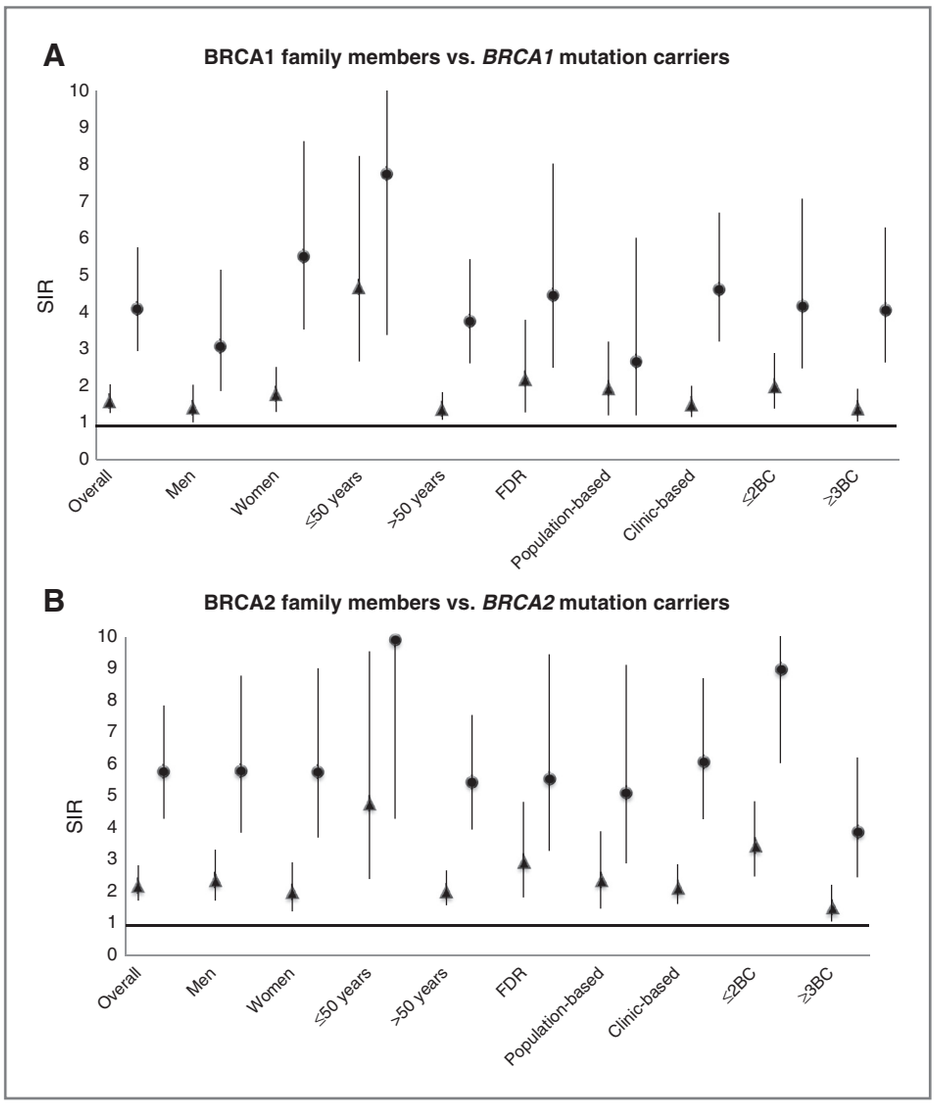

Figure 1. Comparison of SIRs and respective 95% CIs (vertical axis) for all family members (triangles) and weighted by imputed carrier probability (circles) in BRCA1 (A) and BRCA2 (B) families, by class of family (horizontal axis).

pancreatic cancer (OR = 46.5; 95% CI, 9.4–230) for female *BRCA1* or *BRCA2* mutation carriers with an FDR affected with pancreatic cancer compared with those with no FDRs with pancreatic cancer. However, this study was limited by the small number of incidence cases and consequent low precision of the relative risk estimates, especially for the subgroup with a first-degree family history of pancreatic cancer. The authors concluded that the presence of a *BRCA1* or *BRCA2* mutation alone does not justify the adoption of screening for pancreatic cancer, but that this needs to be better investigated in mutation carriers with an FDR affected with pancreatic cancer (17).

To assess whether other factors besides *BRCA1* and *BRCA2* mutations increase the risk of pancreatic cancer in breast cancer families, we analyzed a large number of mutation-negative (BRCAX) families after dividing them into 2 groups, with the first group (class 3) selected for having a larger predicted genetic component (at least 2 early-onset breast cancer cases). Our study estimated a 30% increased overall pancreatic cancer risk and a more than 2-fold increased risk of early onset pancreatic cancer for BRCAX family members. This latter result is lower but consistent with that of an earlier study which estimated a 5.5-fold higher risk of breast cancer diagnosed at age $\leq$50 years in breast cancer families, not due to *BRCA1* or *BRCA2* mutations (26). Class 4 included the largest number of families and was most diverse in terms of number of breast cancer cases per family and age at diagnosis. Compared with the general population, members of these families were at increased risk both of pancreatic cancer overall and of early-onset pancreatic cancer. Results were similar to those for class 3 families, suggesting that the number of relatives with breast cancer did not affect pancreatic cancer risk.

PALB2, a new BC suppressor gene (11, 27, 28), has recently been reported as a pancreatic cancer susceptibility gene (9); germline mutations have been found in approximately 3% of families with $\geq$1 pancreatic cancer

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(10). Of note, 4 of the 5 *PALB2*-related pancreatic cancer families identified to date had ≥1 relative with breast cancer and, in 2 of those families, mutations were seen in individuals with both breast cancer and pancreatic cancer (29). Recent studies reported a prevalence of about 2% of *PALB2* mutations in BRCAX families selected for family history of pancreatic cancer (11, 30), suggesting that other, still unknown, genetic factors likely play a role. Thus, the increased risk of pancreatic cancer among BRCAX families is unlikely to be due to PALB2 mutations segregating in these families.

To assess whether our estimates of pancreatic cancer risk could be affected by the standardized rates used, we carried out an analysis of the risk of another cancer as a control. After a thorough review of the literature, we selected esophageal cancer as suitable for our purpose for 2 main reasons: (i) there is little evidence in the literature supporting an association between this cancer and *BRCA1* and *BRCA2* mutations (31, 32) with only a single recent study reporting an increased risk (31) and (ii) esophageal cancer is a cancer with a strong environmental component, being frequently induced by chronic exposure to environmental risk factors like alcohol and smoking (33). Therefore, we would not expect an increased incidence in our study sample, compared with the general population. Applying an identical analysis to that for pancreatic cancer, no systematic bias away from 1.0 was observed in the SIR for BRCA1, BRCA2, and BRCAX families in the global, nor in the stratified analyses (see Supplementary Table S2).

Our study has some inherent limitations that need to be considered to appropriately interpret our findings. Although the only inclusion criterion applied by sites in the BCFR with clinic-based recruitment was the presence of breast cancer and/or ovarian cancer, there could have been some bias in recruitment, toward families with other cancers (such as pancreatic cancer) previously found associated with genetic predisposition. This could potentially result overestimates of the SIR. However, this is not a major problem as in most of the clinic-based sites, all families that met the study criteria in terms of breast or ovarian cancer, were enrolled in the BCFR. Therefore, we believe it is unlikely that enrollment in the BCFR would be dependent on the presence of cancers other than breast and ovarian.

Another important issue concerns the accuracy of reported pancreatic cancer diagnosis in relatives. A family history of cancer was reported by the proband or her FDRs and, in most cases, it was not verified by clinical reports (19). Validation studies on cancer family history show a low rate of false-positive and false-negative reports of different cancers by FDRs (34–36). Ziogas and colleagues showed that the accuracy of reported cancer family history varies by cancer site; for pancreatic cancer, the positive predictive value (PPV) was 77.4% (95% CI, 58.9–90.4) for FDRs compared with 53.3% (95% CI, 26.6–78.7) for second-degree relatives (36). Our analysis was robust to the stratification for relationship to the proband.

It has been proposed that the method of ascertainment of the proband is a good predictor of accuracy of reported familial cancer data; probands from clinic-based ascertainment sources have been found to be more accurate in their reporting compared with population-based sources, possibly because they are more informed and more motivated about their risk (36). Our results were consistent when the analyses were limited to families recruited through clinic-based settings, suggesting that misdiagnosis of pancreatic cancer did not give rise to spurious results.

The results of the study have potential implications for the screening of pancreatic cancer in high-risk breast cancer families. Currently, screening programs are directed at *BRCA2* mutation carriers and members of breast cancer families with at least one relative affected with pancreatic cancer. Our findings indicate that *BRCA1* mutation carriers also have an increased risk and should therefore also be followed up for pancreatic cancer.

Screening provides the best opportunity to reduce mortality from pancreatic cancer by detecting early-stage cancers, or high-grade pre-neoplastic lesions, such as intraductal papillary mucinous neoplasm (IPMN) and pancreatic intraepithelial neoplasia (PanIN).

Currently, several centers all over the world are conducting screening programs in high-risk individuals; so far, among 988 patients followed-up for pancreatic cancer, 18 pancreatic cancers (1.8%), and 23 PanIN3 or high-grade IPMNs (2.32%) have been diagnosed. However, 22 high-risk individuals (2.22%) were overtreated for low-grade dysplasia or benign tumors. These findings show that screening in high-risk individuals can detect precancerous changes in the pancreas. However, many questions remain, including the identification of the most appropriate screening populations and, most importantly, which criteria for the selection of patients for surgery maximizes benefit and minimizes risk. It is important to clarify that early detection screening for pancreas does not have a clinical value, but it is limited to well-developed research protocols and/or clinical trials.

We also found that members of BRCAX families with at least one relative affected with breast cancer are at increased risk of pancreatic cancer, albeit to a lesser degree than *BRCA1* and *BRCA2* mutation carriers.

In conclusion, carriers of mutations in *BRCA1* or *BRCA2* have an increased risk of developing pancreatic cancer compared with the general population. Members of breast cancer families who test negative for *BRCA1* and *BRCA2* mutations are also at increased risk of pancreatic cancer, although more moderate compared with members of mutation-carrying families. Our study suggests that the increased risk of pancreatic cancer in relatives of breast cancer cases is not fully explained by mutations in *BRCA1* and *BRCA2*.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating BCFR centers, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government or the BCFR.

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