

Elevated Cancer Mortality in the Relatives of Patients with Pancreatic Cancer

Li Wang,¹ Kieran A. Brune,² Kala Visvanathan,^{1,3} Daniel Laheru,³ Joseph Herman,³ Christopher Wolfgang,⁴ Richard Schulick,⁴ John L. Cameron,⁴ Michael Goggins,^{2,3,5} Ralph H. Hruban,^{2,3} and Alison P. Klein^{1,2,3}

¹Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health; Departments of ²Pathology, ³Oncology, ⁴Surgery, and ⁵Medicine, The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins School of Medicine, Baltimore Maryland

Abstract

Most inherited cancer syndromes are characterized by the familial clustering of cancers at several organ sites. To determine if cancers, other than pancreatic cancer, cluster in pancreatic cancer kindreds, we examined mortality patterns among the relatives of National Familial Pancreatic Tumor Registry probands. Over 200,000 person-years of follow-up from 8,564 first-degree relatives of probands and 1,007 spouse controls were included in these analyses. We compared mortality rates of National Familial Pancreatic Tumor Registry participants to US population rates using weighed standardized mortality ratios (wSMR). Analyses were stratified by family history of pancreatic cancer (sporadic versus familial), family history of young onset pancreatic cancer (<50 years), and family history score. Cancer mortality was increased in both the relatives of sporadic probands [wSMR 1.55, 95% confidence interval (95% CI) 1.39-1.73]

and familial probands (wSMR 1.41, 95% CI 1.26-1.58). Relatives of familial probands had a significantly increased risk of dying from breast (wSMR 1.66, 95% CI 1.15-2.34), ovarian (wSMR 2.05, 95% CI 1.10-3.49), and bile duct cancers (wSMR 2.89, 95% CI 1.04-6.39). Relatives of sporadic probands were at increased risk of dying from bile duct cancer (wSMR 3.01, 95% CI 1.09-6.67). Relatives of young onset probands were at higher risk of dying from cancers of the breast (wSMR 1.98, 95% CI 1.01-3.52), colon (wSMR 2.31, 95% CI 1.30-3.81) and prostate (wSMR 2.31, 95% CI 1.14-4.20). Increased cancer mortality was not observed in the spouse controls. Our results show that relatives of pancreatic cancer patients are at higher risk of developing cancers at other sites and highlight the importance of complete family history in clinical risk assessment. (Cancer Epidemiol Biomarkers Prev 2009;18(11):2829-34)

Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the United States (1). Patients with invasive ductal adenocarcinomas of the pancreas, which comprise >90% of all carcinomas of the pancreas, have a 5-year survival rate of <5% (1). Approximately 20% of pancreatic cancer is attributable to cigarette smoking (2, 3). Family history of pancreatic cancer is also a strong risk factor for the disease, with 5% to 10% of patients with pancreatic cancer reporting a close relative with pancreatic cancer (4). The genes responsible for a minority of the familial clustering of pancreatic cancer have been identified, including *STK11*, *CDKN2A*, *PRSS1*, *BRCA2*, and *PALB2* (5-13). Mutations in these genes, with the exception of *PRSS1*, are also associated with an increased risk of cancer of other organs. For example, carriers of germline *CDKN2A* gene mutations have an elevated risk of mela-

noma (12), and carriers of *BRCA2* or *PALB2* gene mutations have an elevated risk of breast cancer (14, 15).

The elucidation of cancer types that coaggregate in families has a number of implications. First, the coaggregation of site-specific cancers suggests a shared genetic susceptibility or shared environmental risk factors. Second, a better understanding of the characteristics of a hereditary cancer syndrome can be used to define more precisely the criteria for that syndrome, as shown by the inclusion of colon, endometrial, small intestine, and ureteral cancers in the Amsterdam criteria for hereditary nonpolyposis colorectal cancer (HNPCC; ref. 16). Finally, including the full spectrum of disease-related cancers is an important aspect of risk assessment and prevention.

Currently, the National Familial Pancreas Tumor Registry at Johns Hopkins is one of the largest registries of familial pancreatic cancer with over 3,185 families enrolled, 1,089 of which are *familial pancreatic cancer kindreds* (defined as at least a pair of first-degree relatives with pancreatic cancer in the family). Prospective studies of families enrolled in this registry have shown that apparently healthy members of familial pancreatic cancer kindreds have a 9-fold increased risk of developing pancreatic cancer themselves (17). However, the risk of extrapancreatic malignancies in these kindreds remains poorly defined.

A common limitation of family studies is that cancer incidence in at-risk relatives is often underreported (18).

Received 6/9/09; revised 8/17/09; accepted 8/25/09; published OnlineFirst 10/20/09.

Grant support: NCI Specialized Programs of Research Excellence grant in gastrointestinal cancer CA62924 and RO3 CA123474, Cigarette Restitution Fund of Maryland, International Collaborative Genetics Research Training Program D43 TW06176, and Sol Goldman Pancreatic Cancer Research Center.

Requests for reprints: Alison P. Klein, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, School of Medicine, 1550 Orleans St, Baltimore, MD 21231. Phone: 4109553511; Fax: 4106140671. E-mail: aklein1@jhmi.edu

Copyright © 2009 American Association for Cancer Research.

doi:10.1158/1055-9965.EPI-09-0557

In the current study we overcame this hurdle by supplementing reported family history data with data from the National Death Index (NDI) maintained by the National Center for Health Statistics (NCHS). Incorporating data from the NDI has been shown to be an accurate way to obtain vital status and cause of death data on cohort study participants in the United States (19). When cause of death coding from nosologists was compared with site-specific cancer mortality data from the NDI, the NDI had a 99% consistency rate (19-21).

The goal of the current study was to identify and quantify mortality from extrapancreatic cancers in familial and sporadic pancreatic cancer kindreds and to determine if mortality rates differ by the strength of family history of pancreatic cancer.

Materials and Methods

Study Population. This study was approved by the Institutional Review Board of Johns Hopkins Medical Institutions, and informed consent was obtained. The details of National Familial Pancreatic Tumor Registry (NFPTR) recruitment methods have been published elsewhere (17). In brief, patients treated for pancreatic cancer at Johns Hopkins Hospital are recruited either by an in-person visit or by mail. In addition, individuals with a personal or family history of pancreatic cancer can either self-refer through an internet site⁶ or they can be referred by a non-Hopkins health care provider. Questionnaire data obtained from the patient or their proxy (spouse or child) includes race, sex, date of birth, type and age at diagnosis of any pancreatic disease, type and age at diagnosis of any cancers, smoking status, and date and cause of death (if deceased). These data are collected on first-degree and some second-degree relatives of the affected proband. Families are contacted annually by mail to obtain updated health information.

The data set for the current study was limited to the 1,328 families who enrolled before December 31, 2004, because at the time of this study NDI data were available for 1979 to 2004. Analyses were limited to the 15,463 individuals with at-least one first-degree relative with pancreatic cancer, because information on more distant relatives was not uniform. We also excluded all pancreatic cancer probands ($n = 2,191$), individuals with missing date of birth ($n = 2,279$), and individuals ($n = 2,429$) who died before January 1, 1979. Probands were defined as individuals reported to have pancreatic cancer on the initial questionnaire and included three individuals who were found, after examination of the pathology records, to have bile duct carcinoma. Among the 8,564 individuals included in the analyses, 2,305 (26.91%) were relatives of patients treated at Johns Hopkins Hospital.

To estimate the effect of excluding individuals with missing dates of birth on our analysis, we assessed the proportion of these individuals that were likely to have been alive within the study period (1979-2004). Under the conservative assumption that parents are exactly 20 years older than their children, we estimated >70% of the individuals with missing date of birth data would have been born before 1900 and 87% before 1920. Given

the average life expectancy for individuals born in 1900 was 47.6 years, only a small proportion of these individuals would have contributed any follow-up time to our analyses.

Our final data set consisted of 8,564 relatives and 1,007 spouse controls. Follow up began on January 1, 1979 and ended at their date of death or December 31, 2004.

Deaths and causes of death were identified by linking records with the NDI and by family report. An NFPTR participant was considered to match an individual listed in the NDI if the name, date of birth, and date of death on record in the NFPTR matched those in the NDI database. Questionable matches were reviewed by examining other data including Social Security Number or place of last residence. The overall match rate was 86.1% for known deceased individuals who were submitted to NDI. Underlying causes of death were grouped based on the International Classification of Diseases, Nine Revision, Clinical Modification (ICD-9-CM) and Tenth Revision, Clinical Modification (ICD-10-CM) codes provided by the NDI.

Statistical Analyses. The strength of family history of pancreatic cancer was classified using three methods: (a) individuals were classified as members of familial pancreatic cancer or sporadic pancreatic cancer kindreds, (b) individuals were classified as having or not having a young onset pancreatic cancer (<50) in their kindred, and (c) individuals were classified based on their tertile of family history score. The family history score for the i th family was calculated as (22):

$$FH_i = \frac{\sum_j O_{ij} - \sum_j E_{ij}}{\sqrt{\sum_j E_{ij}(1-E_{ij})}}$$

For each family member j , O_{ij} is an indicator of pancreatic cancer status at enrollment and E_{ij} is their expected risk of pancreatic cancer calculated by multiplying 5-year age, sex, race, calendar year-specific US cancer incidence rates from the Surveillance Epidemiology and End Results (SEER) database (23) by person-years at risk. Person-years at risk were summed from birth until age of diagnosis of pancreatic cancer or age at death, whichever occurred first. For the years before 1973, 1973 rates were used.

Standardized mortality ratios (SMR) were calculated as the ratio of observed (O) to expected (E) number of deaths, where the expected rates were obtained by SEER multiplying 5-year age, sex, race, and calendar-specific rates for the years 1979 to 2004 by the person-years at risk. Exact confidence intervals based upon a Poisson distribution were used when there were fewer than 100 observed deaths, otherwise a normal approximation was used (24).

Cause of death data was missing on 13% of known decedents. Because this can cause an underestimation of the cause-specific mortality, weighed SMRs (wSMR) were calculated. In brief, for wSMRs the crude SMR and confidence interval are adjusted by the proportion decedents with known cause of death (p). For details, see Rittgen and Becker (25) to obtain the wSMR methodology.

Date of death was not available for 146 individuals. Three methods of imputing date of death were explored: (a) substituting the median age at death of NFPTR cohort members with the same decade of birth and cause of death, (b) substituting the SEER median site-specific age

⁶ <http://pathology.jhu.edu/pancreas/NFPTR.php>

Table 1. Demographics at registry enrollment

	No. individuals	Person-years	Age (mean \pm SD)	Gender		Race	
				Male	Female	Caucasian	Non-Caucasian
First degree relatives	8,564	183,422	60.1 \pm 22.3	4074 (47.6)	4490 (52.4)	8035 (93.8)	529 (6.2)
Pancreatic cancer family history							
Sporadic	4,356	93,525	59.4 \pm 22.4	2056 (47.2)	2300 (52.8)	4045 (92.9)	311 (7.1)
Familial	4,208	89,897	60.8 \pm 22.1	2018 (48.0)	2190 (52.0)	3990 (94.8)	218 (5.2)
Young onset kindred							
Pancreatic cancer in relative before age 50	1,372	29,082	54.7 \pm 23.6	668 (48.7)	704 (51.3)	1302 (94.9)	70 (5.1)
Pancreatic cancer in relative at or after age 50	7,192	154,340	61.1 \pm 21.8	3406 (47.4)	3786 (52.6)	6733 (93.6)	459 (6.4)
Family history score tertile							
Low (range -0.20 to 6.14)	2,875	61,176	64.7 \pm 22.0	1357 (47.2)	1518 (52.8)	2698 (93.8)	177 (6.2)
Medium (range 6.16-9.14)	2,882	61,522	60.4 \pm 22.5	1392 (48.3)	1490 (51.7)	2716 (94.2)	166 (5.8)
High (range 9.15-73.10)	2,807	60,724	55.0 \pm 21.2	1325 (47.2)	1482 (52.8)	2621 (93.4)	186 (6.6)
Spouse controls	1,007	22,411	68.4 \pm 13.5	463 (46.0)	544 (54.0)	968 (96.1)	39 (3.9)

at death for cancer deaths or median age of death of the US general population for noncancer deaths, (c) imputing age at death using birth year, sex, cause of death and family history score (PROC MI, SAS 9.2). Given that all three imputation methods yielded similar results only results using the first approach are presented.

Analyses were limited to cancer sites with at least 10 observed cases. All tests were two-sided. SAS Version 9.2 (SAS Institute, Inc.) was used for all statistical analyses.

Results

A total 183,422 person-years from 8,564 individuals with at least one first-degree relative with pancreatic cancer from 1,321 families were included in these analyses, as were 22,411 person-years from 1,007 spouse controls (Table 1). The average number of relatives per family was 6.5 with a SD of 3.4 and ranging in size from 1 to 29 individuals. There were a similar number of participants and person-time from familial (4,356 individuals, 93,525 person-years) and sporadic (4,208 individuals, 89,897 person-year) kindreds, and there were slightly more females (4,490 individuals, 97,642 person-years) than males (4,074 individuals, 85,780 person-years). 93.8% of relatives and 96.1% of spouse controls reported Caucasian ancestry.

The mean age of the at-risk family members was 60.1 (SD 22.3) years at enrollment. The spouse controls were older, with mean age of 68.4 years (SD13.5). Approximately, 16% of all of the participants included in the study were from kindreds with a young onset pancreatic cancer, defined as having a relative who developed pancreatic cancer before the age of 50 years. It is estimated that ~5% to 10% of all pancreatic cancers occur before the age of 50 (26). Among the 8,564 individuals included in the analyses, 2,305 (26.91%) were relatives of patients treated at Johns Hopkins Hospital. About half, 56.6% of the relatives of young onset patients were from familial pancreatic cancer kindreds and 55.1% were from kindreds in the highest tertile of family history score. Eight percent of families reported mortality due to multiple nonpancreatic cancers.

All Cause and Extrapancreatic Cancer Mortality. The unweighed SMR and wSMR for all-cause and cancer-specific deaths among the first-degree relatives of the pancreatic cancer patients are presented in Table 2. Among the 8,564 relatives of patients with pancreatic cancer, there were a total of 2,440 deaths, significantly fewer than expected in the general US population [wSMR 0.86, 95% confidence interval (95% CI) 0.83-0.89]. All-cause mortality was also significantly lower among the spouse controls (wSMR 0.68, 95% CI 0.60-0.76). Although all-cause mortality was lower than expected, we did observe excess extrapancreatic cancer mortality in relatives of patients with pancreatic cancer (wSMR 1.48, 95% CI 1.36-1.61). The extrapancreatic cancer mortality was not elevated in the spouse controls (wSMR 0.96, 95% CI 0.74-1.23).

To further examine mortality from extrapancreatic cancers in relatives of patients with pancreatic cancer, we stratified our analyses by family history of pancreatic cancer (Table 3). We classified family history in three ways, familial versus sporadic kindreds, presence versus absence of a young onset (<50 years) case of pancreatic cancer in the family, and tertile of family history score. Overall the distribution of family history score ranged from -0.20 to 73.10.

The median and range for each tertile of family history score was 4.74 (-0.20 to 6.14), 7.46 (6.16-9.14), and 12.02 (9.15-73.10), respectively.

Breast and Ovarian Cancer Mortality in Females. Relatives of individuals with familial pancreatic cancer had a significantly elevated risk of dying due to breast cancer (wSMR 1.66, 95% CI 1.15-2.34). Excess breast cancer mortality was also observed in the relatives of young onset cases (wSMR 1.98, 95% CI 1.01-3.52) and among individuals in highest tertile of family history score (wSMR 2.22, 95% CI 1.42-3.33). Breast cancer mortality was not increased in the relatives of late onset cases, in relatives of patients with sporadic pancreatic cancer, nor in individuals in the lowest and middle tertile of family history score. Familial pancreatic cancer kindred members also had a significantly increased risk of dying from ovarian cancer (wSMR 2.05, 95% CI 1.10-3.49).

Colon Cancer Mortality. Excess colon cancer mortality was observed in relatives of patients with young onset

Table 2. SMRs (weighted and unweighted) and 95% CI for all cause and site-specific cancer mortality

	First-degree relatives												Spouse controls		
	All				Male				Female				O	E	wSMR
	O	E	SMR	wSMR	O	E	wSMR	wSMR	O	E	wSMR				
All cause	2,440	2,838	0.86 (0.83-0.89)	0.86 (0.83-0.89)	1,260	1,475	0.85 (0.81-0.9)	0.85 (0.81-0.9)	1,180	1,364	0.87 (0.82-0.92)	0.87 (0.82-0.92)	277	409	0.68 (0.6-0.76)
Extrapancreatic cancers	815	614	1.33 (1.24-1.42)	1.48 (1.36-1.61)	435	336	1.44 (1.29-1.61)	1.44 (1.29-1.61)	380	278	1.52 (1.36-1.71)	1.52 (1.36-1.71)	91	108	0.96 (0.74-1.23)
Breast	59	50	1.18 (0.9-1.52)	1.36 (1.02-1.79)	—	—	—	—	59	50	1.36 (1.02-1.79)	1.36 (1.02-1.79)	6	82	0.83 (0.29-1.89)
Ovarian	23	16	1.44 (0.91-2.16)	1.66 (1.04-2.53)	—	—	—	—	23	16	1.66 (1.04-2.53)	1.66 (1.04-2.53)	1	2.7	0.42 (0.01-2.45)
Colon	71	64	1.1 (0.86-1.39)	1.28 (0.98-1.64)	40	32.5	1.42 (1.00-1.97)	1.42 (1.00-1.97)	31	31.8	1.13 (0.75-1.62)	1.13 (0.75-1.62)	13	10	1.48 (0.75-2.64)
Melanoma	12	8.4	1.43 (0.74-2.5)	1.65 (0.84-2.93)	8	5.2	1.78 (0.76-3.56)	1.78 (0.76-3.56)	4	3.2	1.44 (0.39-3.76)	1.44 (0.39-3.76)	1	1.5	0.76 (0.02-4.41)
Lung	159	179	0.89 (0.76-1.04)	1.02 (0.86-1.20)	104	115	1.04 (0.84-1.27)	1.04 (0.84-1.27)	55	63	1.01 (0.75-1.33)	1.01 (0.75-1.33)	28	354	0.09 (0.06-0.14)
Esophagus	11	12	0.92 (0.46-1.64)	1.06 (0.52-1.93)	9	9	1.16 (0.52-2.23)	1.16 (0.52-2.23)	2	3	0.77 (0.09-2.83)	0.77 (0.09-2.83)	2	2.4	0.95 (0.11-3.57)
Stomach	16	17	0.94 (0.54-1.53)	1.09 (0.61-1.79)	10	10	1.16 (0.55-2.16)	1.16 (0.55-2.16)	6	6.6	1.05 (0.38-2.32)	1.05 (0.38-2.32)	2	2.7	0.84 (0.1-3.18)
Liver	16	9.7	1.65 (0.94-2.68)	1.91 (1.07-3.14)	9	6.3	1.65 (0.74-3.18)	1.65 (0.74-3.18)	7	3.4	2.38 (0.94-4.98)	2.38 (0.94-4.98)	0	1.7	0.67 (0.02-3.89)
Bile duct	12	4.7	2.55 (1.32-4.46)	2.95 (1.5-5.24)	6	2.3	3.01 (1.09-6.67)	3.01 (1.09-6.67)	6	2.3	3.01 (1.09-6.67)	3.01 (1.09-6.67)	0	0.8	0 (0-5.47)
Bladder	16	15	1.07 (0.61-1.73)	1.23 (0.69-2.03)	11	11	1.16 (0.57-2.1)	1.16 (0.57-2.1)	5	4.5	1.28 (0.41-3.04)	1.28 (0.41-3.04)	3	2.5	1.36 (0.27-4.16)
Brain	15	13.7	1.09 (0.61-1.81)	1.26 (0.7-2.12)	8	7.5	1.23 (0.52-2.47)	1.23 (0.52-2.47)	7	6.2	1.3 (0.52-2.73)	1.3 (0.52-2.73)	1	2.5	0.45 (0.01-2.64)
Kidney	11	13.1	0.84 (0.42-1.5)	0.97 (0.48-1.76)	7	8.2	0.99 (0.39-2.06)	0.99 (0.39-2.06)	4	4.9	0.94 (0.25-2.45)	0.94 (0.25-2.45)	—	—	—
Prostate	45	42	1.07 (0.78-1.43)	1.24 (0.89-1.68)	45	42	1.24 (0.89-1.68)	1.24 (0.89-1.68)	6	10	0.69 (0.25-1.53)	0.69 (0.25-1.53)	9	6.8	1.5 (0.66-2.98)
Leukemia	24	24	1.00 (0.64-1.49)	1.16 (0.73-1.75)	18	14	1.49 (0.87-2.39)	1.49 (0.87-2.39)	15	12.6	1.38 (0.76-2.31)	1.38 (0.76-2.31)	3	3.9	0.87 (0.17-2.67)
Lymphoma	25	27	0.93 (0.6-1.37)	1.07 (0.68-1.6)	10	14.1	0.82 (0.39-1.53)	0.82 (0.39-1.53)	6	5.3	1.31 (0.47-2.89)	1.31 (0.47-2.89)	3	4.6	0.74 (0.15-2.26)
Myeloma	12	11.3	1.06 (0.55-1.86)	1.23 (0.62-2.18)	6	6	1.16 (0.42-2.56)	1.16 (0.42-2.56)	6	6	1.16 (0.42-2.56)	1.16 (0.42-2.56)	6	2.0	3.41 (1.2-7.75)

Abbreviations: O, observed deaths; E, expected deaths; —, not available.

pancreatic cancer (wSMR 2.31, 95% CI 1.30-3.81) and in individuals in the highest family history score (wSMR 2.15, 95% CI 1.38-3.19).

Bile Duct Cancer Mortality. Bile duct cancer mortality was significantly elevated in both familial and sporadic pancreatic cancer kindreds (wSMR 3.01, 95% CI 1.09-6.67 and wSMR 2.89, 95% CI 1.04-6.39, respectively). Bile duct cancer mortality was elevated for relatives of patients with late onset pancreatic cancer but not for relatives of young onset patients. A similar trend was observed for family history score, where mortality due to bile duct cancer was elevated for all groups but only statistically significantly elevated for individuals in the lowest tertile of family history score (wSMR 3.85, 95% CI 1.52-8.06).

Prostate Cancer Mortality. We did not observe excess mortality due to prostate cancer in relatives of familial and sporadic pancreatic cancer kindreds. However, relatives of young onset pancreatic cancer patients were at higher risk of dying from cancer of the prostate (wSMR 2.31, 95% CI 1.14-2.40).

Liver, Lung, and Melanoma Cancer Mortality. Excess mortality due to liver cancer was observed for relatives of patients with late onset pancreatic cancer and for those in the highest tertile of family history score (wSMR 2.06, 95% CI 1.14-3.46 and wSMR 4.2, 95% CI 1.79-8.41, respectively).

Whereas overall lung cancer mortality was not higher than expected compared with the general US population, there was a significant excess of lung cancer deaths among individuals in the highest tertile of family history score (wSMR 1.51, 95% CI 1.12-2.00).

Mortality due to melanoma was elevated in all subgroups except those in the middle tertile of family history score; however, these increases in melanoma mortality were not statistically significant.

Discussion

Our results indicated that individuals with a family history of pancreatic cancer are at an increased risk of cancer-related mortality. We have previously showed a 2-fold increased risk of pancreatic cancer in first-degree relatives of patients with sporadic pancreatic cancer, and a 9-fold increased risk of pancreatic cancer in first-degree relatives of patients with familial pancreatic cancer (17).

Here we show that, in addition to an increased risk of pancreatic cancer, individuals with a family history of pancreatic cancer have an increased risk of dying from breast, ovarian, colon, prostate, liver, and bile duct cancers. For breast, ovarian, and colon cancers, the risk increases as the individual's family history of pancreatic cancer increases, suggesting a shared genetic predisposition.

The association of breast and ovarian cancers with pancreatic cancer is not surprising. Pancreatic, breast, and ovarian cancers share susceptibility genes, such as *BRCA2* and *PALB2*. Germline *BRCA2* gene mutations account for 6% to 19% of familial pancreatic cancers, and these mutations increase the risk of breast, pancreatic, and ovarian cancers (5-8). Similarly, we have recently showed that germline *PALB2* gene mutations are the second most common cause of the familial clustering of pancreatic cancer (3).

Approximately 3% of familial pancreatic cancer patients carry germline truncating variants in the *PALB2* gene (27), and germline *PALB2* gene mutations increase the risk of both pancreatic and breast cancer (27). Thus there seems to be a well-defined genetic basis for at least some of the coaggregation of breast and pancreatic cancer in families.

The observed coaggregation of pancreatic cancer and colon cancer may be due to an increased risk of pancreatic cancers among individuals with HNPCC syndrome; however, the risk of pancreatic cancer in HNPCC kindreds remains poorly defined (28). There have been anecdotal reports of pancreatic cancers in HNPCC kindreds, and studies of medullary carcinomas of the pancreas have shown that medullary pancreatic cancers that are microsatellite unstable (*MSI*⁺) can be associated with a family history of cancer (29). However, the majority of families in the current study, reporting both pancreatic cancer and colon cancer, do not meet the Amsterdam or Bethesda guidelines for HNPCC; therefore, it is unlikely that mutations in these genes explain a significant fraction of the observed coaggregation of colon and pancreatic cancer.

The findings of an increased risk of breast and colon cancer among the relatives of young onset pancreatic cancer patients is supported by a recent study that showed pancreatic cancer patients with a family history (first- or second-degree relative) of breast, ovarian, or colon cancers were on average younger than pancreatic cancer patients without a family history of these cancers (30).

Germline mutations in the *CDKN2A* gene are associated with familial melanoma and pancreatic cancer (12). *CDKN2A* mutations are relatively rare, and so it is not surprising that, although we did observe an increased risk of melanoma in our families, this increase was not statistically significant.

In addition to cancers of the breast, ovary, and colon, we also found increased mortality from bile duct cancer in relatives of patients with pancreatic cancer. The excess of bile duct cancer in both the relatives of familial and sporadic pancreatic cancer patients could be due to a shared environmental and/or a common genetic component. However, given the intrapancreatic location of the distal common bile duct and the resultant difficulty in distinguishing distal bile duct and pancreatic adenocarcinomas, misclassification could also explain some of this association. It should be noted, however, that the increased risk of bile duct cancer persisted when analysis as limited to intrahepatic bile duct carcinomas (wSMR 3.38, 95% CI 1.34-7.07). Ascertainment bias could also play a role in that families may have perceived that pancreatic and bile duct cancers are related and are thereby more likely to participate in our research study if they have a family history of pancreatic and bile duct cancer. Individuals with bile duct cancer who were initially reported to have pancreatic cancer were treated as probands and excluded from the analysis.

Despite the excess in cancer mortality observed in our families and our ability to obtain extensive death records through the NDI, all cause mortality was 18% lower in our study population compared with the general US population. One potential explanation for this decreased risk is that NFPTR participants have a healthier life-style and/or higher socioeconomic status than the SEER population. High socioeconomic status has been associated with lower mortality compared with the lower income groups

Table 3. wSMRs and 95% CI for all and cancer-specific cause of death by family characteristics

Cause of death	Family history		Youngest age at onset		Family history score tertile		
	Family kindreds		<50 y	≥50 y	Low	Medium	High
	Sporadic kindreds	Familial kindreds					
All cause	0.86 (0.81-0.91)	0.86 (0.81-0.91)	1.00 (0.90-1.11)	0.84 (0.8-0.88)	0.71 (0.66-0.76)	0.87 (0.81-0.93)	1.16 (1.08-1.25)
Extrapancreatic cancers	1.55 (1.39-1.73)	1.41 (1.26-1.58)	1.52 (1.23-1.85)	1.47 (1.35-1.61)	1.27 (1.11-1.44)	1.38 (1.2-1.58)	2.03 (1.77-2.33)
Breast	1.06 (0.66-1.62)	1.66 (1.15-2.34)	1.98 (1.01-3.52)	1.26 (0.91-1.71)	1.16 (0.69-1.81)	0.95 (0.51-1.62)	2.22 (1.42-3.33)
Ovarian	1.28 (0.58-2.48)	2.05 (1.10-3.49)	2.75 (0.88-6.52)	1.50 (0.87-2.4)	1.24 (0.49-2.6)	2.14 (1.01-4.00)	1.73 (0.63-3.83)
Colon	1.19 (0.81-1.70)	1.33 (0.93-1.86)	2.31 (1.30-3.81)	1.13 (0.84-1.5)	1.04 (0.67-1.54)	1.00 (0.59-1.58)	2.15 (1.38-3.19)
Melanoma	1.65 (0.60-3.65)	1.65 (0.6-3.65)	1.93 (0.23-7.07)	1.58 (0.75-2.96)	1.7 (0.54-4.03)	0.83 (0.10-3.03)	2.63 (0.84-6.23)
Lung	1.05 (0.82-1.33)	1.00 (0.78-1.27)	1.06 (0.66-1.62)	1.02 (0.84-1.22)	0.81 (0.59-1.07)	0.97 (0.71-1.29)	1.51 (1.12-2.00)
Esophagus	0.58 (0.12-1.72)	1.54 (0.65-3.08)	1.16 (0.14-4.24)	1.04 (0.47-2.01)	1.16 (0.37-2.74)	1.16 (0.31-3.01)	0.77 (0.09-2.83)
Stomach	1.24 (0.56-2.39)	0.95 (0.38-1.99)	0.00 (0.00-1.97)	1.27 (0.72-2.10)	1.54 (0.73-2.88)	0.61 (0.12-1.81)	0.94 (0.19-2.78)
Liver	1.89 (0.80-3.78)	1.89 (0.8-3.78)	0.89 (0.02-5.03)	2.06 (1.14-3.46)	1.13 (0.30-2.93)	1.4 (0.38-3.64)	4.20 (1.79-8.41)
Bile duct	3.01 (1.09-6.67)	2.89 (1.04-6.39)	1.93 (0.05-10.9)	3.10 (1.52-5.64)	3.85 (1.52-8.06)	2.17 (0.44-6.43)	2.31 (0.28-8.48)
Bladder	0.46 (0.09-1.35)	1.90 (1.00-3.30)	0.58 (0.01-3.27)	1.28 (0.71-2.15)	0.63 (0.17-1.65)	1.36 (0.49-3.01)	2.24 (0.81-4.95)
Brain	1.36 (0.58-2.72)	1.17 (0.46-2.45)	1.73 (0.35-5.15)	1.17 (0.60-2.09)	0.64 (0.13-1.91)	1.47 (0.53-3.26)	1.12 (0.23-3.32)
Kidney	0.89 (0.28-2.11)	1.05 (0.38-2.32)	1.28 (0.15-4.71)	0.92 (0.41-1.77)	0.83 (0.22-2.15)	1.05 (0.28-2.73)	1.12 (0.23-3.32)
Prostate	1.29 (0.80-1.97)	1.19 (0.73-1.83)	2.31 (1.14-4.20)	1.08 (0.73-1.53)	0.99 (0.57-1.58)	1.38 (0.78-2.28)	1.67 (0.82-3.04)
Leukemia	1.35 (0.73-2.3)	0.96 (0.45-1.8)	0.00 (0.00-1.35)	1.31 (0.82-1.98)	1.20 (0.59-2.18)	0.99 (0.39-2.06)	1.24 (0.45-2.74)
Lymphoma	0.96 (0.47-1.74)	1.20 (0.64-2.04)	0.99 (0.20-2.94)	1.10 (0.68-1.69)	0.50 (0.16-1.19)	1.90 (1.05-3.19)	0.92 (0.29-2.17)
Myeloma	0.83 (0.22-2.15)	1.62 (0.69-3.25)	0.77 (0.02-4.36)	1.30 (0.64-2.36)	0.92 (0.25-2.40)	1.22 (0.33-3.16)	1.85 (0.5-4.81)

after controlling for age, sex, race, urbanity, and education (31). High socioeconomic status has also been associated with lower cancer mortality risk (32). If this is the case, the relative risk estimates we obtained may, in fact, underestimate the true risk to relatives of pancreatic cancer patients in the general population.

The large registry-based nature of our study population allowed us to assess and directly compare the risk of other cancers in relatives of both familial and sporadic pancreatic cancer patients. We were able to minimize bias by verifying date and cause of death using the NDI Plus service. Our analyses were limited to mortality because of our ability to obtain high-quality cause of death data from NDI. Previous studies have shown severe underreporting of cancer incidence in relatives, which causes a downward bias in risk estimates. However, the use of mortality instead of incidence data does have some limitations. SMRs only provide an estimate of relative incidence. For example, if there was higher incidence but longer survival from a particular cancer type, the use of mortality data may not detect this increase due to the associated lower mortality.

In summary, our study suggests that relatives of patients with pancreatic cancer have a higher risk of dying from cancers at other sites. In particular, relatives of patients with familial pancreatic cancer have an increased risk of dying from breast, colon, and ovarian cancer. These data can help to inform genetic counseling and screening recommendations for high-risk families.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

References

- Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin* 2008;58:71–96.
- Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. *Langenbecks Arch Surg* 2008;393:535–45.
- Blackford A, Parmigiani G, Kensler TW, et al. Genetic mutations associated with cigarette smoking in pancreatic cancer. *Cancer Res* 2009;69:3681–8.
- Lowenfels AB, Maisonneuve P. Risk factors for pancreatic cancer. *J Cell Biochem* 2005;95:649–56.
- Murphy KM, Brune KA, Griffin C, et al. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%. *Cancer Res* 2002;62:3789–93.
- Hahn SA, Greenhalf B, Ellis I, et al. BRCA2 germline mutations in familial pancreatic carcinoma. *J Natl Cancer Inst* 2003;95:214–21.
- Goggins M, Schutte M, Lu J, et al. Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. *Cancer Res* 1996;56:5360–4.
- Couch FJ, Johnson MR, Rabe KG, et al. The prevalence of BRCA2 mutations in familial pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2007;16:342–6.
- Whitcomb DC, Gorry MC, Preston RA, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene [see comments]. *Nat Genet* 1996;14:141–5.
- Whitcomb DC, Preston RA, Aston CE, et al. A gene for hereditary pancreatitis maps to chromosome 7q35. *Gastroenterology* 1996;110:1975–80.
- Goldstein AM, Chan M, Harland M, et al. High-risk melanoma susceptibility genes and pancreatic cancer, neural system tumors, and uveal melanoma across GenoMEL. *Cancer Res* 2006;66:9818–28.
- Goldstein AM, Fraser MC, Struwing JP, et al. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations. *N Engl J Med* 1995;333:970–4.
- Su GH, Hruban RH, Bansal RK, et al. Germline and somatic mutations of the STK11/LKB1 Peutz-Jeghers gene in pancreatic and biliary cancers. *Am J Pathol* 1999;154:1835–40.
- Phelan CM, Lancaster JM, Tonin P, et al. Mutation analysis of the BRCA2 gene in 49 site-specific breast cancer families. *Nat Genet* 1996;13:120–2.
- Rahman N, Seal S, Thompson D, et al. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. *Nat Genet* 2007;39:165–7.
- Vasen HF, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). *Dis Colon Rectum* 1991;34:424–5.
- Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer Res* 2004;64:2634–8.
- Kerber RA, Slattery ML. Comparison of self-reported and database-linked family history of cancer data in a case-control study. *Am J Epidemiol* 1997;146:244–8.
- Hunt JR, White E. Retaining and tracking cohort study members. *Epidemiol Rev* 1998;20:57–70.
- Sathiakumar N, Delzell E, Abdalla O. Using the national death index to obtain underlying cause of death codes. *J Occup Environ Med* 1998;40:808–13.
- Doody MM, Hayes HM, Bilgrad R. Comparability of national death index plus and standard procedures for determining causes of death in epidemiologic studies. *Ann Epidemiol* 2001;11:46–50.
- Yang Q, Khoury MJ, Rodriguez C, Calle EE, Tatham LM, Flanders WD. Family history score as a predictor of breast cancer mortality: prospective data from the Cancer Prevention Study II, United States, 1982–1991. *Am J Epidemiol* 1998;147:652–9.
- Surveillance EaERP. SEER*Stat Database: Incidence SEER 9 Regs, Nov 2002 Sub (1973–2000). released April 2003, based on the November 2002 submission ed: National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch; 2003.
- Breslow NE, Day NE. *Statistical Methods in Cancer Research*. Lyon (France): World Health Organization, IARC; 1987.
- Rittgen W, Becker N. SMR analysis of historical follow-up studies with missing death certificates. *Biometrics* 2000;56:1164–9.
- Raimondi S, Maisonneuve P, Lohr JM, Lowenfels AB. Early onset pancreatic cancer: evidence of a major role for smoking and genetic factors. *Cancer Epidemiol Biomarkers Prev* 2007;16:1894–7.
- Jones S, Hruban RH, Kamiyama M, et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. *Science* 2009;324:217.
- Aarnio M, Sankila R, Pukkala E, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. *Int J Cancer* 1999;81:214–8.
- Wilentz RE, Goggins M, Redston M, et al. Genetic, immunohistochemical, and clinical features of medullary carcinoma of the pancreas: a newly described and characterized entity. *Am J Pathol* 2000;156:1641–51.
- McWilliams RR, Bamlet WR, Rabe KG, Olson JE, de Andrade M, Petersen GM. Association of family history of specific cancers with a younger age of onset of pancreatic adenocarcinoma. *Clin Gastroenterol Hepatol* 2006;4:1143–7.
- Lantz PM, House JS, Lepkowski JM, Williams DR, Mero RP, Chen J. Socioeconomic factors, health behaviors, and mortality: results from a nationally representative prospective study of US adults. *JAMA* 1998;279:1703–8.
- Ward E, Jemal A, Cokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. *CA Cancer J Clin* 2004;54:78–93.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association
for Cancer Research

Elevated Cancer Mortality in the Relatives of Patients with Pancreatic Cancer

Li Wang, Kieran A. Brune, Kala Visvanathan, et al.

Cancer Epidemiol Biomarkers Prev 2009;18:2829-2834. Published OnlineFirst October 20, 2009.

Updated version Access the most recent version of this article at:
doi:[10.1158/1055-9965.EPI-09-0557](https://doi.org/10.1158/1055-9965.EPI-09-0557)

Cited articles This article cites 30 articles, 8 of which you can access for free at:
<http://cebp.aacrjournals.org/content/18/11/2829.full#ref-list-1>

Citing articles This article has been cited by 6 HighWire-hosted articles. Access the articles at:
<http://cebp.aacrjournals.org/content/18/11/2829.full#related-urls>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
<http://cebp.aacrjournals.org/content/18/11/2829>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.