Published in final edited form as:
J Gastrointest Cancer. 2007 ; 38(2-4): 119–126. doi:10.1007/s12029-008-9022-2.

Risk of other cancers in individuals with a family history of pancreas cancer

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Abstract

Background—Inherited predisposition to pancreas cancer accounts for approximately 10% of cases. Familial aggregation may be influenced by shared environmental factors and shared genes. We evaluate whether a family history of pancreas cancer is a risk factor for ten specified cancers in first-degree relatives: bladder, breast, colon, head & neck, lung, lymphoma, melanoma, ovary, pancreas and prostate.

Methods—Risk factor data and cancer family history were obtained for 1816 first-degree relatives of pancreas cancer case probands (n=247) and 3157 first-degree relatives of control probands (n=420). Unconditional logistic regression models using generalized estimating equations were used to estimate odds ratios (ORs) and 95% confidence intervals of having a first-degree relative a specified cancer.

Results—A family history of pancreas cancer was associated with a doubled risk of lymphoma (OR = 2.83, 95% CI = 1.02–7.86) and ovarian cancer (OR = 2.25, 95% CI = 0.77–6.60) among relatives after adjustment. Relatives with a family history of early-onset pancreas cancer in a proband had a 7-fold increased risk of lymphoma (OR = 7.31, 95% CI = 1.45 – 36.7). Relatives who ever smoked and had a family history of pancreas cancer had a 5-fold increased risk of ovarian cancer (OR = 4.89, 95% CI = 1.16–20.6).

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Conclusion—Family history assessment of cancer risk should include all cancers. Assessment of other known and suspected risk factors in relatives will improve risk evaluation. As screening and surveillance methods are developed, identifying those at highest risk is crucial for a successful screening program.

Keywords

pancreas cancer; lymphoma; ovarian cancer; family history of pancreas cancer; smoking; young age at cancer diagnosis; genetic risk

Introduction

It is estimated that in 2007, there will be 37,170 new cases of pancreas cancer diagnosed, and 33,370 deaths from pancreas cancer [1]. Pancreas cancer is rapidly fatal, with a median survival of approximately 6 months after diagnosis [2]. Over 75% of pancreas cancers are diagnosed in regional or distant stages, leading to the dismal 5-year relative survival rate of 5% [3]. Risk factors for pancreas cancer include increasing age, cigarette smoking, a history of diabetes or pancreatitis, and a family history of pancreas cancer [4–6]. Inherited predisposition to pancreas cancer accounts for approximately 10% of all cases [7].

Familial aggregation of pancreas cancer has been reported in various populations[8–11], including the families in this current study [12]. Familial clustering of pancreas or other cancers may be influenced by shared environmental factors and by shared genes. Here, we evaluate whether a positive family history of pancreas cancer is a risk factor for ten specified cancers in first-degree relatives: bladder, breast, colon, head & neck, lung, lymphoma, melanoma, ovary, pancreas and prostate. Additionally, we examine whether younger age of the proband at pancreas cancer diagnosis and whether the relatives' positive smoking history further increases risk of other cancers.

Methods

The study was approved by the local institutional review boards and written informed consent was obtained from each individual proband participating in the study. Probands were selected from a case-control study of pancreas cancer conducted from October 1, 1996 through March 31, 1999. We use the term proband to indicate the person from whom the family history of cancer was obtained. Case probands were recruited by contacting eight hospital pathology departments, medical records departments, various oncology and surgical physician groups and tumor registries in Southeastern Michigan. Eligible case probands were between the ages of 30 and 79 years, were residents of 18 counties (Hillsdale, Lenawee, Monroe, Jackson, Washtenaw, Wayne, Ingham, Livingston, Oakland, Macomb, Shiawassee, Genesee. Lapeer, St. Clair, Bay, Gratiot, Midland or Saginaw) at the time of diagnosis, were English-speaking and could be contacted by phone. Because the median survival time for patients with pancreas cancer was short, a rapid case finding system was used in the participating hospitals and physician offices. Only those patients who had newly diagnosed adenocarcinoma of the exocrine pancreas (topography codes C25.0–C25.3 and C25.7), confirmed by pathologic criteria, were included in the study.

Of the 358 patients who were eligible for the study, 53 died before contact could be made and 37 were not contacted because of physician refusal. Of the remaining 268 case probands who were invited to participate in the study, 247 (92%) agreed. Control probands were frequency matched to case probands by age group (30–44, 45–59, 60–69, 70–79 years), gender, race, (African-American, Caucasian and other) and county of residence (counties were grouped into nine different areas based on population size and proximity to each other). In addition, eligible

control probands were English-speaking and could be contacted by phone. Random digit dialing techniques based on the Waksberg method were used to recruit control probands [13]. Of the 550 people invited to participate in the study, 420 (76%) agreed. Characteristics of the case and control probands (age range, gender and ethnicity) were comparable and are reported elsewhere [12].

Data Collection

Trained interviewers conducted in-person interviews with the probands to collect data regarding first-degree family history of ten selected cancers (bladder, breast, colon, head & neck, lung, lymphoma, melanoma, ovary, pancreas and prostate). Data collected on all first-degree relatives (parents, siblings and offspring) included the age of each relative at interview date or at death, gender, history of selected cancers, history of "other" cancer(s), age at cancer diagnosis or age at death for every reported cancer. In addition, history of diabetes, and cigarette smoking status (more than 100 cigarettes in lifetime) was collected on each relative.

The interviewer also requested proband demographic information (age, gender, ethnicity, marital status, educational level, annual income), cigarette smoking history, personal history of selected medical conditions and personal exposure history (residential and occupational) to selected chemicals. Data were double entered and algorithms were created and employed to detect out of range values, logical errors and omissions in the database.

Statistical Analysis

The analyses treated each first-degree relative of a case proband or control proband as a study subject. These subjects were then categorized as being related to a case proband or a control proband. To determine whether risk of other cancer varied with relationship to a case or control proband (i.e., a family history of pancreas cancer in a first-degree relative), unconditional logistic regression models using generalized estimating equations (GEEs), that take into account family correlation structures were used to estimate odds ratios and confidence intervals. The models were adjusted for the age, sex, and smoking status of the subject, and the age (at diagnosis or interview (<60, ≥ 60)), race and smoking status of the proband. The outcome variable in the models was the specified cancer in the study subjects. For those cancers with a significant or marginally significant association with pancreas cancer in a proband, two-level interactions of family history of pancreas cancer with smoking status (ovarian cancer) or age of proband (lymphoma) were evaluated. Individuals with missing data for any of the variables were excluded from the analyses. All statistical tests were two-sided and all analyses were performed by SAS version 8.0 (Cary, NC).

Results

A total of 247 pancreas cancer case probands and 420 control probands were interviewed, resulting in 1,991 first-degree relatives of case probands and 3,286 first degree relatives of control probands. Complete data was available for 1,816 relatives of case probands (91.2%) and 3,157 relatives of control probands (96.1%). The distribution of reported cancers among these 4,973 subjects is depicted in Table 1. Of the 10 cancer sites specifically asked for each relative, risk of lymphoma (OR=2.83, 95% CI=1.02–7.86) and pancreas (OR=2.49 95% CI=1.32–4.69) cancer were statistically significantly associated with having a family history of pancreas cancer (i.e., being a relative of a case proband) compared to being a relative of a control proband, after adjusting for each subject's age, sex, smoking status, the age of the proband at diagnosis or interview (<60, ≥ 60), proband race and proband smoking status. Risk for ovarian cancer was increased among relatives of pancreas case probands versus relatives

of control probands, but the results were not statistically significant (OR=2.25, 95% CI=0.77–6.60).

Further analyses of subjects with lymphoma and ovarian cancer are presented in Table 2. The distribution of the relationship type (i.e., parents, siblings and children) of the relatives of the case probands and control probands were not statistically significantly different, nor were the mean ages of these relatives. The case probands reported 11 first-degree relatives with lymphoma (5 parents, 5 siblings, and 1 offspring) compared to 6 relatives with lymphoma in control subjects (3 parents, 2 siblings and 1 offspring). After accounting for multiple occurrences of lymphoma in families, 3.6% (9/247) of case probands interviewed reported a first-degree relative with lymphoma compared with 1.4% (6/420) of control probands. There were 11 ovarian cancers reported in case families (4 mothers, 6 siblings, and 1 offspring) compared to 6 ovarian cancers in control relatives (3 mothers, 2 siblings, and 1 offspring). After accounting for multiple occurrences of ovarian cancer in families, 3.2% (8/247) of case probands interviewed reported a first-degree relative with ovarian cancer compared with 1.4% (6/420) of control probands. Individuals with missing data were dropped from the regression models in Table 1, resulting in 2 fewer lymphomas among relatives of case probands (n=9), and 3 fewer ovarian cancers among relatives of case probands (n=8). The overall percentage of affected case and control relatives were not statistically different, and for those affected, the ages at diagnosis were also not statistically different.

We next assessed whether there were two-way interactions between smoking, family history, and age of the proband at diagnosis (for cases) or age at interview (for controls) on risk of lymphoma or risk of ovarian cancer. We found a seven-fold increased risk of lymphoma (OR = 7.31, 95% CI = 1.45–36.7) among relatives of cases with early-onset pancreas cancer (age <60) compared to relatives of older control probands (≥60 years of age at interview) (Table 3). We found a 5-fold increased risk of ovarian cancer (OR = 4.89, 95% CI = 1.16–20.6) among case relatives with a smoking history (ever smoked), compared to never smoking control relatives (Table 4). None of the other subgroups were statistically significant.

Discussion

This study focuses on first-degree relatives of pancreas cancer cases and includes each subject's smoking status, age, diabetes and cancer history. As previously reported, we identified increased risk of pancreas cancer in first-degree relatives of patients with pancreas cancer [12]. This current analysis also suggests that those with a family history of pancreas cancer in a first-degree relative may be at greater risk for lymphomas compared to those without a family history of pancreas cancer. Statistically significant increased risk of ovarian cancer was also seen in ever smoking women with a family history of pancreas cancer compared to never smoking women without a family history of pancreas cancer

Lymphoma is comprised of two main sub-types: Hodgkin's Disease and Non-Hodgkin's Lymphoma (NHL) [14]. NHL comprises the largest percentage of lymphomas, accounting for 89% of the estimated 71,380 new lymphomas in 2007 [1]. Immunosuppression is a suspected risk factor for NHL, including both acquired and inherited immunodeficiency syndromes (i.e., congenital X-linked immunodeficiency, severe combined immunodeficiency, ataxia-telangiectasia (AT) and Wiskott-aldrich syndrome) [14, 15]. Other risk factors for NLH include infectious agents (HTLV-I, HIV, *H. pylori*), and previous chemotherapy[6, 15–17].

In addition to our study, there is limited evidence supporting or refuting a relationship between increased risk of lymphoma associated with a family history of pancreas cancer. In a case-control study of lymphohematopoetic cancers that included Caucasian men with and without NHL, Pottern et al. reported a fourfold increased risk of NHL among those with a sibling history

of pancreas cancer (OR = 4.4, 95% CI = 1.4 to 14.7), although a parental history of pancreas cancer was not significant [18]. A study of the first-degree relatives of 426 pancreas cases seen at the Mayo Clinic found decreased risk of lymphoma (Standardized incidence ratio, (SIR) =0.28 95% CI=0.12–0.55), including a non-statistically significant decreased risk in relatives of early-onset (proband <60 years) pancreas cancer cases (SIR=0.39 95% CI=0.05–1.42) [19]. This study used population-based Surveillance, Epidemiology and End Results (SEER) data as the reference group, which does not collect information on smoking histories. Another case-control study of 526 men and women with pancreas cancer identified from three population-based cancer registries, with a mix of races and ethnicities more similar to our Michigan population, did not report an association between lymphoma and a family history of pancreas cancer, although it was unclear how many, if any, lymphomas were reported in this population [20]. While epidemiological evidence is inconclusive regarding the familial aggregation of lymphoma and pancreas cancer, risk associated with early-onset pancreas cancer, where we saw the highest risk, should continue to be explored.

Ovarian cancer is the 8th estimated leading cause of cancer-related incidence in 2007 and 5th leading cause of cancer-related mortality among women in the United States[1]. Risk factors include older age, being of Northern European descent, having a family history of ovarian cancer, being part of a family that carries the mutated *BRCA1* or *BRCA2* genes, nulliparity, infertility, and obesity [21]. While we report that a positive family history of pancreas cancer and smoking was associated with increased risk of ovarian cancer, overall, smoking has not been shown to be a risk factor for the majority of ovarian cancers (those of serous or endometrioid origin) although increased risk for mucinous ovarian cancer has been suggested among heavy smokers [22, 23].

The first report of familial aggregation of pancreas and ovarian cancers was from a study of 662 women diagnosed with primary ovarian cancer ascertained from the Utah Cancer Registry [24]. Through linkage to the Utah Population Database, Kerber et al. reported that a family history of pancreas cancer accounted for 4.8% of ovarian cancer cases and that having any first-degree relative with pancreas cancer was associated with increased risk of ovarian cancer (OR=2.88, 95% CI 1.57–5.28) [24]. A population-based case-control study in a more racially diverse population reported a similar association between ovarian and pancreas cancers. Individuals with a family history of ovarian cancer had a statistically significant increased risk of pancreas cancer (RR=5.3, 95% CI = 1.4 to 20.2) [20]. It should be noted that this study did not evaluate the contribution of smoking habits of the relatives when evaluating familial aggregation of ovarian and pancreas cancers.

Laboratory studies provided etiological evidence supporting the association between pancreas and ovarian cancers, when, in 1995, Schutte et al. reported a homozygous deletion at the *BRCA2* locus in pancreas carcinoma, leading to the localization of the *BRCA2* gene later that year [25, 26]. Germline mutations in *BRCA2* have been reported in approximately 10% of sporadic pancreas carcinomas [27]. In a study performed at the Johns Hopkins Medical Institutions of pancreas cancer patients with familial pancreas cancer (defined as at least two affected first-degree relatives), 17% of individuals had *BRCA2* mutations [28]. A similar study done in Europe yielded remarkably similar findings, with 19% of individuals with familial pancreas cancer harboring *BRCA2* mutations [29]. In 173 families with known *BRCA2* mutations identified in Europe and North America, there was a 3.5-fold risk of pancreas cancer (RR=3.51 95% CI 1.87–6.58) [30]. A smaller study of 139 *BRCA2* families in the Netherlands reported a 6-fold relative risk (RR=5.9, 95% CI=3.2–10) [31]. We did not see an increased risk of breast cancer in our study population. While neither the American College of Medical Genetics nor the United States Preventive Services Task Force has issued recommendations regarding genetic testing for *BRCA2* mutations with respect to pancreas cancer, testing for *BRCA2* mutations and

mutations in other cancer associated genes has been suggested for individuals with a family history of pancreas and other cancers [32].

Increased risk of pancreas cancer has been identified in families with other cancer syndromes. Mutations in *BRCA1*, which is associated with increased breast and ovarian cancer risk, may also increase risk of pancreas cancer. In a study of 699 families with known *BRCA1* mutations, individuals with known mutations were 2.26 times more likely to have pancreas cancer than those who did not carry mutations [33]. Other syndromes also transmitted in the autosomal dominant fashion that have been associated with risk of pancreas cancer include Peutz-Jeghers syndrome [34], familial atypic multiple mole melanoma (FAMMM) syndrome [35, 36], familial adenomatous polyposis[37] and possibly hereditary nonpolyposis colorectal cancer (HNPCC) [38]. An autosomal recessive disorder has also been associated with increased risk of pancreas cancer. Lymphomas, ovarian, pancreas and breast cancers are part of the ataxia-telangiectasia genetic syndrome[39, 40]. This syndrome is the result of defects in the ataxia telengectasia mutated gene (*ATM*) and results in impaired DNA double-strand break response [41]. While homozygous mutations in *ATM* are rare, (approximately 1 of every 40,000 live births in the US), individuals with heterozygous mutations (approximately 1% of the population) may also be at increased risk of certain cancers [42]. While these known syndromes account for a small proportion of the attributable risk of pancreas cancer, it is likely other genes that influence risk have yet to be identified. Examining other cancers in families with a history of pancreas cancer may provide important insight into the genetic mechanisms involved in carcinogenesis.

Our study had a number of methodological strengths. We obtained data from in-person interviews with newly diagnosed incident case probands. In-person interviews provide for the collection of more reliable and detailed information than self-administered questionnaires or telephone interviews [43]. We also enumerated each first degree relative and collected specific information (age, diabetes and smoking status) regardless of whether or not the individual had cancer. Our family-based study design allowed a more comprehensive assessment of familial aggregation of cancer than is possible in a simple case-control study. In addition, we had high participation among case probands and control probands. In order to determine how successful our case identification was, we assessed the thoroughness of our case finding mechanisms for Wayne, Oakland, and Macomb counties by searching the metropolitan Detroit population-based Surveillance, Epidemiology and End Results registry to identify eligible case probands at participating hospitals who had been missed. We found only three such case probands, indicating that substantial selection bias in case ascertainment was unlikely. Lastly, we included only those case probands with histological confirmation of adenocarcinoma of the exocrine pancreas.

Our study also had several limitations. Our findings are restricted to relatives of cases who were diagnosed between the ages of 18 and 79. Our response rate of 69% among the cases, while high for a population-based study of a rapidly fatal cancer is not representative of pancreas cancer cases diagnosed at age 80 and above, and may also not fully represent all younger cases. Additionally, we relied on the proband to report information about each first-degree relative's age, smoking habits, history of diabetes, and history of cancer. While proxy reporting has been found to be reliable for cancers [44, 45] and smoking [46], there is still potential for recall bias. Recall bias regarding family history of cancer may have contributed to an overestimate of risk because the case probands may have been more attuned than the control probands to their families' cancer experience. Although we did not verify diagnoses in the relatives, we did collect information on several types of cancers among the first-degree relatives of the probands. The proportion and ranking of reported cancers in relatives by the pancreas cancer case probands was similar to the proportion and ranking of reported cancers in relatives by the control probands. For example, approximately 30% of cancers reported in first-degree relatives of case probands were breast cancer compared with 29% in control probands. Prostate

cancer reporting in case relatives and control relatives was also similar (20% and 22%, respectively) as were colon cancers (15% of cancers were colon cancer reported by case probands versus 14% in control probands). Thus, recall bias by the case probands is unlikely to have played a major role. Case probands were also somewhat less likely to completely report all of the information regarding their relatives' smoking status, diabetes status, or age. Individuals with missing data were dropped from the regression models, resulting in 2 fewer lymphomas among case relatives (n=9), and 3 fewer ovarian cancers among case relatives (n=8), while no cases were dropped from control families. Therefore, risk estimates may be somewhat conservative. Lastly, we asked specifically about 10 cancers, and then asked the proband about any other diagnosed cancers. Due to the differing methods, we did not include any cancers reported from the open-ended question in the analysis. We were also not able to obtain any specific histological information about the cancers (i.e. NHL versus Hodgkin's Lymphoma). It should also be noted that the risk estimates often represent a limited number of cancers among both the case and control relatives, resulting in large confidence intervals. These findings should be considered hypothesis-generating in nature, rather than conclusive evidence of elevated risk of disease.

Conclusion

Pancreas cancer is a rapidly fatal disease for which earlier intervention is greatly needed. Family history assessment should include all other cancers, in addition to pancreas cancer. Assessment of other known and suspected risk factors in relatives (such as smoking status) will also improve risk assessment for relatives of pancreas cancer cases. Although there is no formal screening program recommended for those at high risk of pancreas, lymphoma or ovarian cancers, clinicians can use family history information to strongly encourage individuals to adopt healthier lifestyles (i.e. smoking cessation, dietary changes) and to seek appropriate medical care. In addition, as screening methods and surveillance techniques are developed for these and other cancers, identifying those at highest risk is crucial for a successful screening program. Future research exploring the genetic and environmental interactions associated with lymphomas, ovarian cancer and pancreas cancer may identify additional risk factors or serve to better define what proportion of seemingly sporadic cancers are actually due to inherited predisposition.

Acknowledgments

This research was supported by the National Institute of Environmental Health Sciences RO1 ES07129 and the National Cancer Institute RC25-CA7716 and NO1-CN-65064, and by gifts from the Schreiber Foundation for Cancer Research, the Marlin Pemberton Fund, and a gift in memory of Adrian Mayer, MD. "The original publication is available at www.springerlink.com".

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Table 1

Risk estimates of cancers in first degree relatives of pancreas cancer case probands and control probands

Cancer Site	Cancers in relatives of case probands		Cancers in relatives of control probands		Adjusted OR[a] (95% CI)
	Yes	No	Yes	No	
All Cancers	234	1589	389	2786	1.01 (0.84, 1.22)
Lymphoma [c]	9	1814	6	3169	**2.83 (1.02, 7.86)**
Pancreas [b]	23	1793	16	3141	**2.49 (1.32, 4.69)**
Ovary	8	870	6	1534	2.25 (0.77, 6.60)
Head and Neck	18	1805	22	3153	1.41 (0.74, 2.68)
Colon	30	1793	39	3136	1.19 (0.72, 1.98)
Female Breast	35	843	62	1478	0.93 (0.60, 1.45)
Melanoma [c]	13	1810	25	3150	0.89 (0.36, 2.20)
Lung	30	1793	62	3113	0.85 (0.53, 1.36)
Urinary Bladder	6	1817	12	3163	0.84 (0.31, 2.31)
Prostate	23	922	44	1591	0.83 (0.49, 1.42)

[a] Note: Adjusted by first-degree relative's age, sex, smoking status, proband's age (<60, >=60), race and ever smoking status.

[b] Adjusted by variables in [a] and diabetes.

[c] The model is not adjusted by race because all the cancers occurred in the same race (Caucasian).

Table 2

Characteristics of Family Members of Case Probands and Control Probands

	No.	Mean Age	No. with Lymphoma	Mean age at Dx[a]	No. with Ovarian Cancer	Mean age at Dx[a]
Relatives of Case Probands						
All Family Members	1991	53.5	11	48.1	11	52.3
First Degree Relatives						
Parents	518	72.7	5	54.4	4	63.8
Siblings	760	57.6	5	45.6	6	49.0
Offspring	713	35.5	1	29.0	1	26.0
Relatives of Control Probands						
All Family Members	3286	51.7	6	47.7	6	46.5
First Degree Relatives						
Parents	840	70.8	3	55.0	3	58.0
Siblings	1263	55.4	2	56.0	2	43.0
Offspring	1183	34.4	1	32.5	1	19.0

[a]Note: Mean age at diagnosis only was calculated for those relatives with specific cancer

Table 3

Interaction between family history of pancreas cancer and age at diagnosis or interview of the proband on the risk of lymphoma in first degree relatives of pancreas cancer case probands and control probands

Relative Cohort	Proband's age at pancreas cancer diagnosis or interview	Lymphoma		OR (95% CI)
		Yes	No	
Control Relative	≥60	2	2011	1.00
Control Relative	< 60	4	1269	2.79 (0.52, 15.2)
Case Relative	≥60	4	1293	3.32 (0.61, 18.1)
Case Relative	< 60	6	585	**7.31 (1.45, 36.7)**

Table 4

Interaction between smoking and family history of pancreas cancer on the risk of ovarian cancer

Relative Cohort	Relative smoking history	Ovarian Cancer		OR (95% CI)
		Yes	No	
Control Relative	Never	3	943	1.00
Control Relative	Ever	3	613	1.73 (0.33, 9.11)
Case Relative	Never	3	571	1.68 (0.35, 8.14)
Case Relative	Ever	8	359	**4.89 (1.16, 20.6)**