# Pancreatic Cancer Genetic Epidemiology Consortium

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## Abstract

**We have organized the Pancreatic Cancer Genetic Epidemiology (PACGENE) Consortium to identify susceptibility genes in familial pancreatic cancer (FPC). The Consortium comprises seven data collection centers, a statistical genetics core, and a pathology/archival genotyping core. We recruit kindreds containing two or more affected blood relatives ascertained through incident pancreatic adenocarcinoma cases, physician referrals, and/or through Internet recruitment. Accrual to a database containing core clinical, demographic, lifestyle, and family history information from questionnaires is ongoing, along with biospecimen collection. To date, 13,147 patients have been screened for family history, of whom 476 (50% male) probands and 1,912 of their adult (99% unaffected) relatives have been enrolled. Of these, 379 kindreds meet criteria for FPC, having at least two first-degree relatives with pancreatic cancer. Cumulative incidence curves using available age of diagnosis (onset) among and affected relatives were compared with those for incident pancreatic cancer cases reported to 13 U.S. Surveillance Epidemiology and End Results (SEER) sites from 1973 to 2000 ($N$ = 72,700). The mean age ± SD at diagnosis among 466 PACGENE probands and 670 affected relatives was 64.1 ± 11.8 and was 65.4 ± 11.6 for the subset of 369 FPC probands and 429 relatives. Both samples were significantly younger than the mean age at diagnosis in the SEER population (70.0 ± 12.1 years; differences in curves versus SEER, $P < 0.001$). Age at diagnosis (excluding probands) in FPC kindreds does not decrease with increasing number of affected individuals. In our sample, younger age at diagnosis was observed whether we grouped probands by recruitment sites that predominantly recruited through high-risk referrals, or through screening all pancreatic cancer patients for family history. Linkage studies are ongoing. The PACGENE Consortium will be a valuable family-based resource that will greatly enhance genetic epidemiology research in pancreatic cancer.** (Cancer Epidemiol Biomarkers Prev 2006;15(4):704–10)

## Introduction

Pancreatic cancer is an enigmatic cancer, although it is the fourth most common cause of cancer death in the United States. In 2005, there will be an estimated 32,180 new cases and 31,800 deaths reported in the United States (1), and the Surveillance Epidemiology and End Results (SEER) program reports an overall age-adjusted incidence rate of 11 per $10^5$ (2). African Americans have a higher incidence rate (14.9 per $10^5$) than Caucasians (10.9 per $10^5$), and the incidence of pancreatic cancer is higher among men (12.5 per $10^5$) compared with women (9.8 per $10^5$; ref. 2). Ninety-five percent of pancreatic neoplasms are ductal adenocarcinomas, and 80% of patients with ductal adenocarcinoma present with metastatic disease, leading to an extremely poor 5-year survival rate of 4% (3). To date, the three most consistent risk factors reported for pancreatic cancer are older age, cigarette smoking, and a family history of the disease (3, 4). These findings underscore the role of both genes and environment in the development of pancreatic cancer and have spurred further research.

Several lines of investigation (family clustering, case-control studies, and cohort studies) have provided impetus for conducting more extensive genetic epidemiologic investigations. Although about 90% of pancreatic cancer patients report a negative family history of pancreatic cancer, familial clustering in the remaining 5% to 10% of the disease (presumably attributed to inheritance of moderate or high penetrance genes) has been reported (5-9). Formal case-control investigations provide persuasive evidence that a family history of pancreatic cancer is a risk factor, and some have further elaborated the role of cigarette smoking or age at diagnosis of pancreatic cancer in the family setting. In a Canadian sample, 7.8% of 179 pancreatic cancer cases and only 0.6% of 179 controls had a family history of pancreatic cancer, a 13-fold difference, with no differences in environmental risk factors between the two groups (10). An increased risk of pancreatic cancer was reported among relatives of 363 Italian cases compared with relatives of 1,234 controls [odds ratio, 2.8; 95% confidence interval (95% CI), 1.3-6.3], after adjusting for tobacco, dietary factors, and history of diabetes or pancreatitis (11). Pancreatic cancer risk was higher among close relatives of 362 pancreatic cancer patients in Louisiana compared with 1,408 controls (odds ratio, 5.25; 95% CI, 2.08-13.21; ref. 12), and a multicenter U.S. study of 484 cases and 2,099 controls found that relatives of individuals with pancreatic cancer have 3.2-fold (95% CI, 1.8-5.6) increased odds of developing pancreatic cancer compared with relatives of controls, even after adjusting for age at diagnosis/interview, geographic area, and gender. Relatives of individuals with pancreatic cancer who were long-term smokers (defined as being smokers for >20 years) had an odds of developing pancreatic cancer of 5.3 (95% CI, 2.1-13.4) compared with 2.2 (95% CI, 1.0-7.9) among relatives of pancreatic cancer cases who were not long-term smokers (13). A southeast Michigan study of 247 cases and 420

Received 9/20/05; revised 1/20/06; accepted 2/14/06.

**Grant support:** National Cancer Institute grant R01 CA97075, Mayo Clinic Specialized Programs of Research Excellence in Pancreatic Cancer grant P50 CA102701, and Lustgarten Foundation grant LF033.

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doi:10.1158/1055-9965.EPI-05-0734

controls reported a relative risk of 8.23 for pancreatic cancer among smokers who had a first-degree relative diagnosed before 60 years of age (95% CI, 2.18-31.07), and a relative risk of 2.15 among nonsmokers with a comparable family history (95% CI, 0.63-7.27). Having a family history of pancreatic cancer diagnosed at any age increased the risk of pancreatic cancer 2.49-fold (95% CI, 1.32-4.69; ref. 14). A recent study of 426 unselected sequential Mayo Clinic patients with pancreatic adenocarcinoma and 3,355 of their first-degree relatives obtained standardized incidence ratios using SEER data. Overall, the standardized incidence ratio for pancreatic cancer to first-degree relatives was 1.88 (95% CI, 1.27-2.68), and this risk increased to 2.86 (95% CI, 1.15-5.89) if the proband was <60 years of age at diagnosis (15). Similar findings were observed in a study of the Iceland genealogy database, which evaluated 930 cases among 32,534 at-risk individuals, and yielded a standardized incidence ratio of 2.33 (90% CI, 1.83-2.96) for first-degree relatives (16).

In the American Cancer Society's Cancer Prevention Study II cohort of 1,102,308 individuals, 3,751 prospectively developed pancreatic cancer during 14 years of follow-up. After adjusting for age, the relative risk of developing pancreatic cancer in individuals who reported a positive family history of pancreatic cancer at baseline was 1.5 (95% CI, 1.1-2.1). This risk estimate was unchanged after adjustment for history of gallstones, body mass index, smoking history, alcohol consumption, history of diabetes, and several dietary factors (17). A prospective study of first-degree relatives of FPC cases in the National Familial Pancreatic Tumor Registry found that the standardized incidence ratio was 9.0 (95% CI, 4.5-16.1) for pancreatic cancer compared with the SEER population, whereas for relatives of non-FPC cases the standardized incidence ratio was not significantly increased (18). This risk in FPC kindreds was elevated in individuals with three or more (32.0; 95% CI, 10.2-74.7), two (6.4; 95% CI, 1.8-16.4), or one (4.6; 95% CI, 0.5-16.4) first-degree relative(s) with pancreatic cancer.

Studies of pancreatic cancer in the context of genetic syndromes have yielded further evidence for the role of inherited risk for pancreatic cancer (summarized in Table 1). It is now accepted that familial pancreatic cancer (FPC) is an identifiable entity (kindreds containing at least two affected first-degree relatives), and that genetic predisposition is a plausible explanatory etiology (19, 20). The proportion of FPC explained by mutations in tumor suppressor genes that give rise to familial cancer syndromes is still unclear. Lal et al. reported that 13% of families classified as at high or intermediate familial risk of pancreatic cancer were found to carry *BRCA1*, *BRCA2*, or *p16* germ line mutations (21). Murphy et al. (22) found 17.2% of pancreatic cancer probands with at least two additional blood relatives with pancreatic cancer carry deleterious *BRCA2* mutations. Hahn et al. (23) reported that up to 19% of 26 German FPC patients had either a frameshift mutation or an unclassified variant of the *BRCA2* gene. Interestingly, the Fanconi anemia pathway genes other than *BRCA2* (i.e., *FANCA, FANCC*, and *FANCG*) have little or no role in FPC development (24, 25). Eberle et al. reported a multipoint LOD score of 5.36 for a susceptibility locus for pancreatic cancer on chromosome 4q32-34 in a single multigenerational pedigree, where affected status included pancreatic cancer, dysplasia, or pancreatic insufficiency (26), but most forms of FPC are not associated with pancreatic insufficiency.

**Table 1. Hereditary syndromes and genes associated with pancreatic cancer**

| Syndrome | Gene(s) | Chromosome location | Refs. |
|---|---|---|---|
| Hereditary breast cancer, early onset 2 | *BRCA2* | 13q12 | (19, 21–23, 42) |
| Familial atypical multiple mole melanoma syndrome | *CDKN2A/p16* | 9p21 | (43, 44) |
| Peutz-Jeghers syndrome | *STK11/LKB1* | 19p13 | (45) |
| Fanconi anemia syndrome | *FANCC* | 9q22 | (24, 46, 47) |
| | *FANCG* | 9p13 | |
| Hereditary pancreatitis | *PRSS1* | 7q35 | (48, 49) |
| Hereditary nonpolyposis colorectal cancer | *hMSH2* | 2p15 | (50) |
| | *hMLH1* | 3p25 | |
| | *hPMS2* | 7p1 | |
| | *hMSH6* | 2p16 | |
| Cystic fibrosis (heterozygotes) | *CFTR* | 7q31 | (51) |

Because it is well-known that hereditary forms of breast cancer and colorectal cancer present at a younger age than their sporadic counterparts, it is also plausible that pancreatic cancer patients from FPC pedigrees develop pancreatic cancer at a younger age compared with patients with sporadic pancreatic cancer. Along with the observation that the risk to relatives of developing pancreatic cancer increases as the age at onset of affected relatives decreases (14, 27), FPC has been proposed to be a younger onset cancer (28, 29).

We have assembled the Pancreatic Cancer Genetic Epidemiology (PACGENE) Consortium to investigate formally the genetic basis of FPC using model-based linkage analysis. The model to be used has been developed by segregation analysis of 287 families, where the most parsimonious explanatory model is autosomal-dominant inheritance of a rare major gene or genes influencing age of onset, with reduced penetrance in carriers (27).

Family history screening of many hundreds of pancreatic cancer patients is required to identify the most informative kindreds suitable for linkage analysis of FPC and to obtain adequate numbers of biospecimens (DNA) for genotyping. The effort required to conduct an informative linkage analysis of this magnitude was recently illustrated by the 12-center experience of the Genetic Epidemiology of Lung Cancer Consortium, which screened 26,108 lung cancer patients to identify 771 families that were developed for genetic linkage, and with a final sample of 52 families that were ultimately genotyped (30).

There are many challenges that limit collection of family histories, even more so for pancreatic cancer. These include rapid fatality of pancreatic cancer, early deaths of key informative relatives due to causes other than pancreatic cancer, nonpancreatic cancers, problems in reliability of cancer history, lack of pathology confirmation, false paternity, limited cooperation of patients and physicians in eliciting vital family and pathology information, ethnic and racial differences in clinical research participation, and cultural factors, including diet and lifestyle patterns. The PACGENE Consortium has incorporated study design elements, including prospective and expeditious case identification and family history screening, that help address these challenges and improve our ability to conduct formal genetic epidemiologic studies of pancreatic cancer.

## Materials and Methods

**Structure of the PACGENE Consortium.** The PACGENE Consortium was organized in 2002 with funding from the National Cancer Institute, and data collection is ongoing. Seven data collection sites and two cores form the primary functional units of the Consortium, which is coordinated from Mayo Clinic. The data collection sites are Dana-Farber Cancer Institute (Boston, MA), The Sol Goldman Pancreatic Cancer Research Center at Johns Hopkins University (Baltimore, MD),

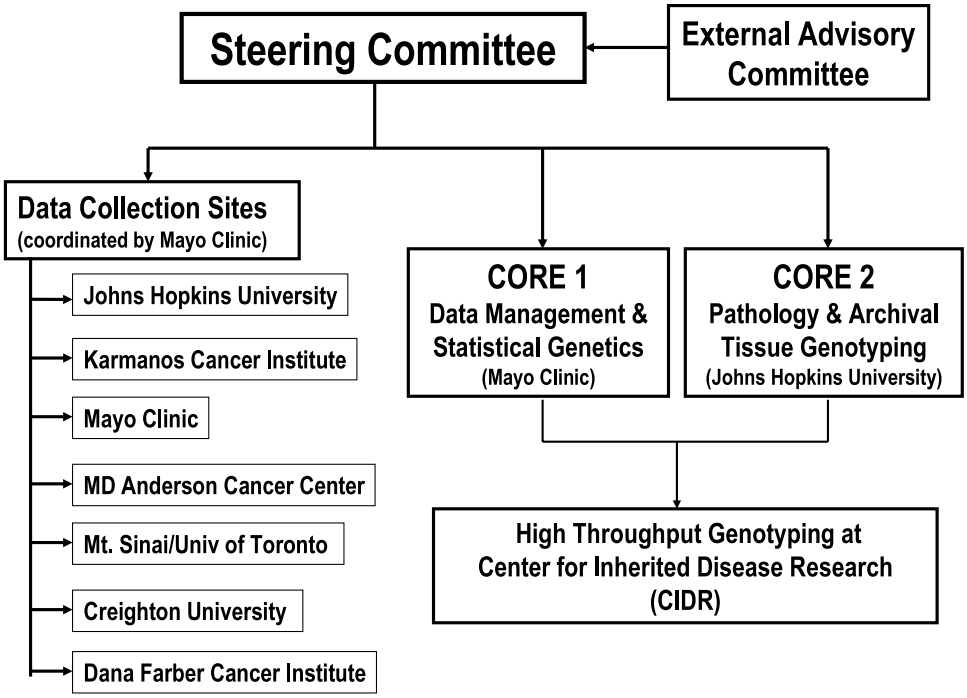


**Figure 1.** Organization of the PACGENE Consortium.

Karmanos Cancer Institute-Wayne State University (Detroit, MI), Mayo Clinic (Rochester, MN), M.D. Anderson Cancer Center (Houston, TX), Creighton University (Omaha, NE), and University of Toronto (Ontario, Canada). Directors of each of these units form the Steering Committee, which governs the consortium's activities and use of the resource. The Statistical Genetics and Data Management Core, located at Mayo Clinic, provides all programming, statistical analysis, and data management for the PACGENE Consortium. The Pathology and Archival Genotyping Core, located at Johns Hopkins University, performs all pathology review, DNA preparation from archival tissue, and tissue genotyping as needed. Genotyping services are largely outsourced to high-throughput facilities, including the Center for Inherited Disease Research, funded by the NIH (31). An External Advisory Committee, composed of individuals with expertise in statistical genetics, epidemiology, surgery, pathology, and advocacy provides advice. Figure 1 depicts the relationship of the PACGENE components.

**PACGENE Probands.** Each data collection site prospectively (and to a lesser extent, retrospectively) identifies probands for the PACGENE registry through any combination of three mechanisms: screening family histories of incident pancreatic cancer patients, physician referrals, and/or through Internet recruitment. Histologic confirmation is sought for primary adenocarcinoma of the pancreas (International Classification of Diseases-Oncology site codes C25.0-C25.3, C25.7, C25.9 and morphology codes 8140/3 and 8140/6; ref. 32) during the registration process, and proband eligibility also includes having at least one blood relative with pancreatic cancer. The date of histologic diagnosis is recorded as the date of diagnosis. Because the clinicians who see pancreatic cancer patients at each site cooperate with the study, patients can often be recruited directly in the clinic setting. At off-site hospitals, physician cooperation and patient consent to be contacted are first obtained. All potential probands complete a family history screening questionnaire, which seeks cancer family history on first-degree, second-degree, and third-degree relatives to establish eligibility for further study as a high-risk family. In our experience, ~10% of newly diagnosed pancreatic cancer patients will report a family history of pancreatic cancer, but due to factors that affect participation (logistics and family issues), a smaller number adequately meet the requirements for further follow-up for the linkage study. If a patient's family history does not contain at least two blood relatives with pancreatic cancer, no further recruitment for the PACGENE Consortium is pursued. All PACGENE sites have received approval from their respective Institutional Review Boards, and all U.S. sites comply fully with health information privacy rules of the Health Insurance Portability and Accountability Act. The PACGENE Consortium has been granted a Certificate of Confidentiality (33) from the National Cancer Institute. Certificates of Confidentiality allow researchers to avoid the involuntary release of any portion of research records containing information that could be used to identify confidential information on study participants.

**PACGENE Family Members.** FPC kindreds are evaluated for suitability for linkage analysis by inspection and also using linkage simulation programs (i.e., SLINK; ref. 34). In the development of PACGENE kindreds, probands (or next of kin if the proband is deceased) are contacted and asked to consent to furnish names and addresses of additional family members, or alternatively to seek consent from family members if they would be willing to participate in the study. Expanded families include available first-degree, second-degree, and third-degree adult relatives of all pancreatic cancer cases plus marry-ins or other relatives who would make the pedigree informative for linkage. Invited relatives are asked to complete their own consent form, family history and risk factor questionnaires, and medical release forms when pertinent to confirm the diagnosis of cancers and to obtain pathology records and archival specimens when needed.

**Data Collection.** In addition to clinical and family history questionnaires, all consenting probands and family members complete a risk factor questionnaire seeking information on demographics (age, sex, ethnicity, and religious heritage), medical history and medications, lifestyle, and possible pancreatic cancer risk factors (alcohol intake, smoking, and occupational exposures). Specific information about cigarette smoking includes ever smoked 100 cigarettes in lifetime

**Table 2. Characteristics of PACGENE Consortium registry data collection sites, numbers of patients screened, probands, and relatives enrolled in registry**

| Data collection site | Year data collection initiated | Recruitment method(s) | No. pancreatic cancer patients screened | No. PACGENE registry probands* | No. PACGENE registry relatives |
|---|---|---|---|---|---|
| Dana-Farber Cancer Institute | 2004 | S, HR | 369 | 10 | 44 |
| Johns Hopkins University | 1994 | S, HR, I | 4,538 | 168 † | 799 |
| Karmanos Cancer Institute | 2001 | S, HR, I | 317 | 21 | 84 |
| Mayo Clinic | 2000 | S, HR, I | 2,038 | 101 | 512 |
| M.D. Anderson Cancer Center | 2002 | S, HR, I | 4,596 | 57 | 99 |
| Creighton University | 1990 | HR | 309 | 56 | 84 |
| University of Toronto | 1998 | S, HR | 980 | 63 | 290 |
| Total | | | 13,147 | 476 | 1,912 |

Abbreviations: S, screen all pancreatic cancer patients for family history at institution; HR, high-risk clinic and physician referrals; I, Internet.
*Pancreatic cancer probands are entered into the PACGENE registry if they have at least one other blood relative with pancreatic cancer and blood sample.
†John Hopkins University pancreatic cancer probands are entered into the PACGENE registry if they have one first-degree relative with pancreatic cancer, and there is a blood sample available on at least one pancreatic cancer case in the family.

(yes/no), age started, age stopped, number of cigarettes per day currently and average number over lifetime, and overall number of years smoked. All data are entered using site-customized programs developed in Progeny, SYBASE, and Microsoft Access, and core data are uploaded quarterly to the PACGENE database created with SYBASE and maintained by the Data Management and Statistical Analysis Core.

Thirty milliliters of blood samples from the proband and other participating family members are obtained and processed immediately at each site's clinical research facility. If participants live at some distance, samples are shipped by overnight express to the requesting site for processing and storage until required for genotyping. Medical records, diagnosis, dates of procedures, and pathology are reviewed and confirmed. If available, we obtain formalin-fixed, paraffin-embedded blocks with tissue for DNA samples from all probands and affected relatives. Archival tissue is requested and stored until ready for processing by the Pathology and Archival Tissue Genotyping Core. Tissue procurement is sensitive to the policies of individual facilities throughout the United States and Canada. DNA is extracted from unstained 10-μm slides after deparaffinizing as previously described (35), and microdissection is done to dissect neoplastic and nonneoplastic tissue (36) for genotyping and future tissue analyses as needed.

**Statistical Analysis of Age of Onset.** Linkage analysis of informative families from the PACGENE registry has been initiated, and results will be reported as they become available. Descriptive statistics are calculated for age of onset of pancreatic cancer for PACGENE probands and their affected relatives reported in the family history survey as well as age at diagnosis of pancreatic cancer in cases from the SEER registry, years 1973 to 2000 (37, 38). Selection from the SEER registry used the Site and Morphology Recode International Classification of Diseases-Oncology, 2nd edition codes C25.0-C25.3, C25.7, and C25.9. Cumulative incidence of age of diagnosis/onset curves were generated using the Kaplan-Meier method (39). The log-rank test was used to test whether there is a significant difference between the cumulative incidence in probands and their affected relatives compared with the SEER registry pancreatic cancer cases and between the number of affected individuals per family.

## Results

**Accruals to Date.** Table 2 summarizes features of the seven data collection sites of the PACGENE Consortium. The sites were inaugurated at varying times since 1990. The number of pancreatic cancer patients screened at each site reflects both the history of the site and the recruitment method (any combination of screening pancreatic cancer patients treated at the institution, high-risk clinic and physician referrals, or the Internet). The PACGENE Consortium sites have screened a total of 13,147 patients and have enrolled 476 probands. These sites have recruited an additional 1,912 relatives (99% unaffected) of the probands, for a total enrollment to date in the PACGENE registry of 2,388 individuals.

**Proband and Pedigree Characteristics.** Available data on 476 probands and their relatives in the PACGENE registry have been used for analyses of proband and pedigree characteristics. Pancreatic carcinoma diagnosis in 52.9% of probands are confirmed by pathology, 6.1% by medical records, and 3.4% by death certificate (confirmation of the remainder is pending). Pancreatic carcinoma diagnosis in

**Table 3. Number of FPC families, mean age ± SD and median age at diagnosis/onset by number of affected first-degree relatives of the proband per pedigree in the PACGENE Consortium**

| No. individuals in pedigree with pancreatic cancer (proband and first-degree relatives) | No. FPC families | Total no. affected individuals* | | Mean age ± SD at diagnosis/onset | | Median age at diagnosis/onset | |
|---|---|---|---|---|---|---|---|
| | | Including probands | Excluding probands | Including probands | Excluding probands | Including probands | Excluding probands |
| 2 | 310 | 584 | 282 | 65.3 ± 12.0 | 66.1 ± 12.3 | 66 | 67 |
| 3 | 51 | 143 | 94 | 65.8 ± 11.5 | 63.9 ± 11.6 | 66 | 65 |
| 4 | 17 | 65 | 48 | 64.8 ± 12.8 | 63.4 ± 13.1 | 67 | 66 |
| 6 | 1 | 6 | 5 | 69.0 ± 6.7 | 67.2 ± 5.6 | 68.5 | 67 |
| Total | 379 | 798 | 429 | 65.4 ± 11.9 | 65.3 ± 12.2 | 66 | 66 |
| PACGENE probands | — | 369 | — | 65.4 ± 11.6 | — | 66 | — |
| SEER reference | — | 72,700 | — | 70.0 ± 12.1 | — | 71 | — |

NOTE: Data for affected individuals are shown including or excluding the probands.
*The totals for PACGENE indicate individuals with known age at diagnosis/onset.

relatives is also an ongoing process. To date, 18.7% of relatives are confirmed by pathology, 5.7% by medical records, and 11.7% by death certificates. Two hundred thirty-eight (50%) of PACGENE probands are male, and mean age ± SD of pancreatic cancer diagnosis is 64.1 ± 11.8 years, with median of 64 and range of 30 to 97 years. Thirty-eight percent are never smokers, 47.1% are ever smokers, and smoking status is unknown on 14.9%. Of the 476 pedigrees in the PACGENE registry, 379 (79.6%) contain at least one pair of affected first-degree relatives, which constitutes the consensus criterion for FPC (19). Table 3 summarizes the FPC families with respect to number of affected individuals per pedigree.

**Age of Diagnosis of FPC.** Distributions of age at diagnosis of pancreatic cancer in the probands and their affected first-degree relatives, the SEER reference population, and by the number of affected individuals in the family are also shown in Table 3. The mean age ± SD at diagnosis among 466 probands in the registry was 64.1 ± 11.8 years and was 65.4 ± 11.6 in 369 FPC probands (probands for whom age of diagnosis was known), whereas the mean age at diagnosis among the SEER population was 70.0 ± 12.1 years. There was also a difference of 5 years between the median age at diagnosis of the FPC probands and the SEER patient population (66 and 71 years, respectively). Among these kindreds, mean ages at diagnosis did not significantly differ when stratified by number of affected individuals in the pedigree.

We generated cumulative incidence (age of diagnosis/onset) curves of pancreatic cancer using available data from all 466 probands and 670 of their affected relatives, and compared these to pancreatic adenocarcinoma incidence reported to 13 U.S. SEER sites from 1973 to 2000 ($N$ = 72,700). The curves for both the probands and relatives differed significantly from the SEER population ($P < 0.001$). Similar results were obtained when restricted to the 369 FPC kindreds, which are shown in Fig. 2.

To address possible sources of bias in ascertainment of the FPC probands, we examined age at diagnosis in two additional ways. First, we compared mean age at diagnosis of probands grouped by recruitment site. Those sites in which recruitment of PACGENE probands is accomplished predominantly by screening family histories of all pancreatic cancer patients seen at their institution (Mayo Clinic, M.D. Anderson Cancer Center, and University of Toronto) formed one group ($N$ = 151), and the other sites that predominantly recruited through high risk referrals formed the second group ($N$ = 218). We

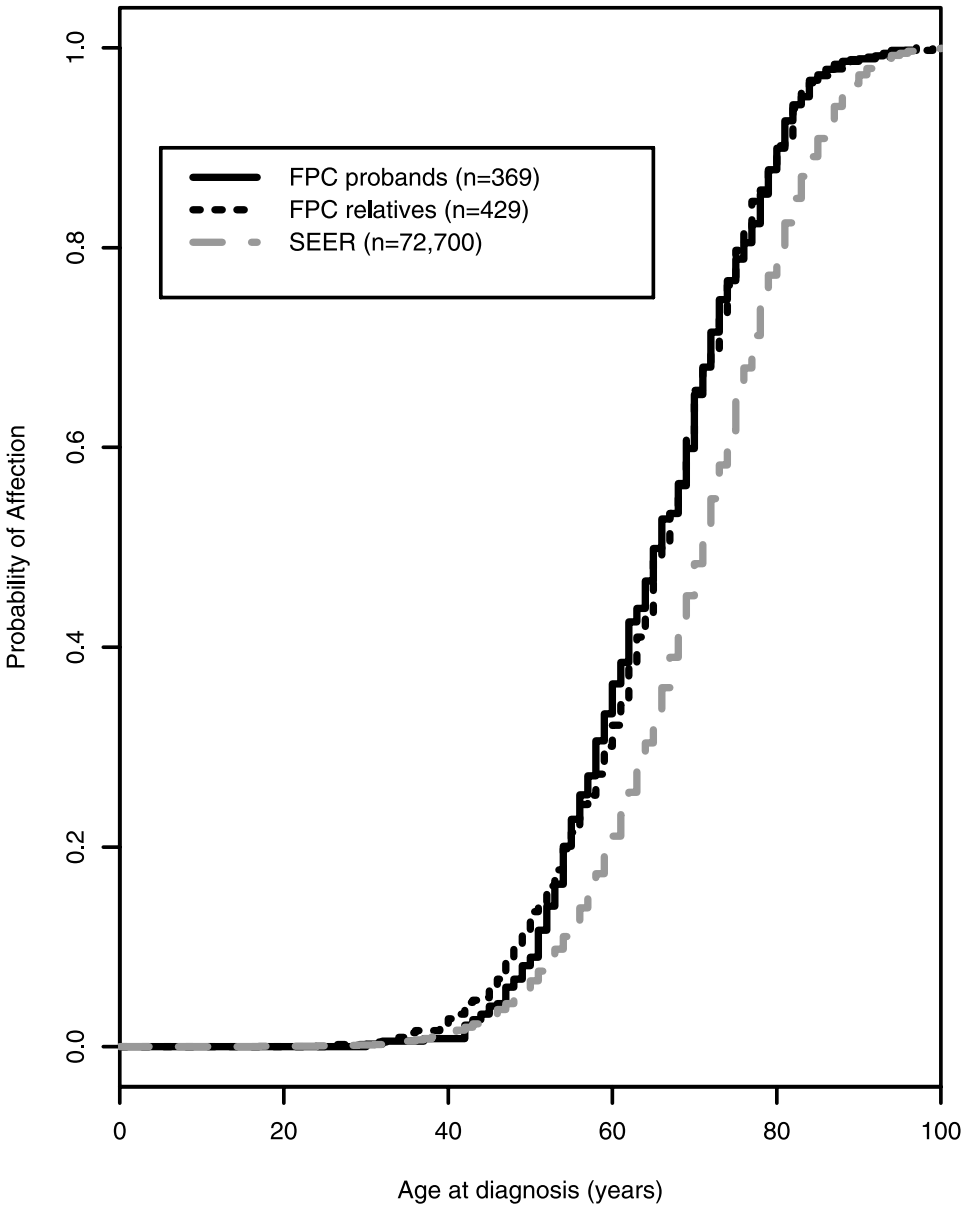


**Figure 2.** Cumulative age at diagnosis of pancreatic cancer in PACGENE's FPC probands, their affected relatives, and in the SEER database, 1973 to 2000. Probands' and relatives' curves each differed significantly from SEER curve ($P < 0.001$).

found that there was no difference in mean age at diagnosis (64.9 ± 11.5 years in the first group, and 65.7 ± 11.7 years in the latter group). Both groups were significantly younger than the SEER population ($P < 0.001$). Second, we evaluated the mean age by type of affected relative. We found that half the FPC probands (mean age, 61.6 ± 11.5 years) were defined by having an affected parent, 36% (mean age, 68.1 ± 10.2 years) by an affected sibling, 4% (mean age, 79.0 ± 11.1 years) by an affected child, and 10% (mean age, 69.4 ± 8.8 years) by a combination of parents, siblings, or children. The FPC probands defined by affected parents and siblings had significantly younger ages at diagnosis compared with SEER ($P < 0.0001$ and <0.0022, respectively). Finally, it may be postulated that our observation is a reflection of decreasing age at diagnosis over time in the general population, represented by the SEER data. We computed the mean ages of pancreatic cancer diagnosis by year and observed that the trend over time in the age of diagnosis within the SEER registry increased from 67.9 years in 1973 to 70.3 years in 2000 ($P < 0.0001$).

## Discussion

We have developed a foundation for studying the genetic basis of pancreatic cancer. The published literature provides substantial evidence that genetic factors play a role in pancreatic cancer, specifically FPC. The PACGENE Consortium, using high-risk FPC kindreds, is designed to investigate the genetic etiology of pancreatic cancer susceptibility. The Consortium consists of seven data collection sites and two support cores that facilitate the accomplishment of its main goals, which are to identify susceptibility genes for pancreatic cancer using model-based linkage analysis and to serve as an infrastructure for further genetic epidemiologic studies of pancreatic cancer. Data accrual is ongoing, and to date, we have screened the family histories of 13,147 pancreatic cancer patients to identify and register 476 probands in the PACGENE database. The results of linkage analysis of FPC pedigrees will be reported as they become available.

We have compared SEER-based data with the available age at diagnosis (onset) of the PACGENE probands and their affected relatives, with a focus on 369 FPC kindreds. These represent the most comprehensive comparisons in the literature to date. Our results show that PACGENE probands have a significantly younger age at diagnosis than pancreatic cancer patients in the general population and support previous studies of age of onset of pancreatic cancer in the setting of FPC that suggest that affected individuals are younger than the sporadic cases of pancreatic cancer (14, 20, 25, 26). However, the differences in our study are modest, ~5 years (when either mean or median ages are compared). These results contrast with the observations of age at onset in other inherited forms of cancer (colorectal or breast cancer), in which the age at diagnosis can differ by one or two decades from sporadic forms of these cancers (40, 41). We conducted additional analyses to address the possibility that our results may be the result of ascertainment biases. We found that there were no differences in mean onset ages when FPC probands were grouped by sites reflecting the predominant mode of ascertainment. Probands from sites that recruited largely through high-risk referrals did not have significantly younger mean onset ages than probands identified through sites that predominantly screened family histories of all pancreatic cancer patients. We also found that half of our FPC probands were defined by having an affected parent, more than a third by having an affected sibling, and that these two proband groups had a significantly younger age at diagnosis compared with SEER cases. Finally, younger age at diagnosis might be reflected in the SEER data themselves, but our analysis showed that the younger age at diagnosis in the PACGENE sample is not an artifact of earlier diagnosis over time in the general population.

Unlike the study conducted by Klein et al. (27), we observed that as the number of affected individuals in the kindred increased, the age at diagnosis decreased only slightly if at all, differences that were not statistically significant (Table 3). Explanation of this unexpected result is not immediately obvious and merits future investigation. Ascertainment of PACGENE families is a mix of self-referral, physician referral, and screening incident cases. Young age at diagnosis in family clusters reported in the literature most likely reflect their selective nature, whereas the PACGENE data include a much broader representation of pancreatic cancer in families. Heterogeneity of age at diagnosis within a family can also be due to phenocopies as well as variation in lifestyle and smoking exposure, which were not addressed in our analyses, but which future investigations will examine as our sample size increases.

The PACGENE Consortium illustrates the value of pooling resources to accomplish a common complex goal. Because of its rapidly fatal nature and the relatively low incidence of this cancer, it is difficult for any single site to accumulate sufficient samples of informative families for a linkage analysis, so that a comprehensive analysis truly requires collaboration. The different sites that are working together in this initiative were initiated at various time points and have had varying levels of success in accruing FPC kindreds. The shared goals and methodologies of data collection of this Consortium will clearly facilitate and accelerate our understanding of the genetic basis of pancreatic cancer. As has been shown by breast cancer and colon cancer gene discovery research, the scientific, clinical, public health, and epidemiologic ramifications of identifying susceptibility genes for pancreatic cancer are certain to dramatically improve our efforts to understand, prevent, and manage pancreatic cancer.

## Note

All PACGENE Consortium sites continue to enroll eligible families and welcome referrals. Please contact Gloria M. Petersen or the coinvestigators at any of the PACGENE sites for further information:

Mayo Clinic: http://mayoresearch.mayo.edu/mayo/research/pacgene/index.cfm.

M.D. Anderson Cancer Center: http://www.mdanderson.org/departments/pancreatic/display.cfm?id=a70b53d7-88ab-11d4-b10c00508b603a14&method=displayfull&pn=79c7ee82-6e2a-11d4-b0e900508b603a14.

Creighton University: http://medicine.creighton.edu/hci/Pancreatic/Available%20Pancreatic%20Studies.htm.

Karmanos Cancer Institute: http://www.karmanos.org/view_news.asp?id=28.

Mt. Sinai Hospital, Toronto: http://www.mtsinai.on.ca/familialgicancer/Diseases/PC/default.htm.

Johns Hopkins University: http://www.pathology.jhu.edu/pancreas/.

Dana-Farber Cancer Institute: http://www.danafarber.org/pat/cancer/gastrointestinal/gi-pages.asp.

## Acknowledgments

We thank the patients and families who have participated in this study; the following members of the PACGENE External Advisory Committee who provided advice and guidance: Joan Bailey-Wilson, Ph.D., Chief of Statistical Genetics Branch (National Human Genome Research Institute, Baltimore, MD); Albert Lowenfels, M.D., Professor of Surgery (New York Medical College, Valhalla, NY); Paula Kim, Founder of Pancreatic Cancer Action Network (Green Cove Springs, FL); James S. Howe, M.D., Professor of Surgery (University of Iowa, Iowa City, IA); David Klimstra, M.D., Associate Attending

Pathologist (Memorial Sloan Kettering Cancer Center, New York, NY); and John Potter, M.D., Ph.D., Professor of Epidemiology (Fred Hutchinson Cancer Center, Seattle, WA); and the following PACGENE study team members at each site: Diane Batzel; Jason Carnahan; Suresh Chari, M.D.; Julie Cunningham, Ph.D.; Jessica Curry; Tamela Dahl, R.N.; Stephen Grimes; Traci Hammer; Wilma Lingle, Ph.D.; Que Luu; Robert McWilliams, M.D.; Janet Olson, Ph.D.; Karen Olson; Curtis Olswold; Kathy Liffrig; and Larry Tordsen (Mayo Clinic); Kieran Brune; Anirban Maitra, M.D.; Connie Griffin, M.D.; Sandy Markowitz (Johns Hopkins University); Carolyn Deters, R.N. and Abdon Trowonou (Creighton University); Ayelet Eppel, M.Sc.; Heidi Rothenmund, M.S.; Kara Smith, M.S.; Saumea Thayalan (Toronto); Phyllis Adatto, Georgina Armstrong, Joyce Brown (M.D. Anderson Cancer Center); Kate Sargent, M.S.; Barbara Rusin, M.S.; Ann Schwartz, Ph.D.; Cecilia Yee, M.S. (Karmanos Cancer Institute); Sarah Hunt and Peter Zumpfe (Dana-Farber Cancer Institute).

## References


1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55:10–30.
2. Ries LAG, Eisner MP, Kosary CL, et al., editors. SEER Cancer Statistics Review, 1975–2002, National Cancer Institute. Bethesda, MD, based on November 2004 SEER data submission, posted to the SEER web site 2005 [cited 2006 Jan 12]. Available from: http://seer.cancer.gov/csr/1975_2002/.
3. Yeo TP, Hruban RH, Leach SD, et al. Pancreatic cancer. Curr Probl Cancer 2002;26:176–275.
4. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. Lancet 2004;363: 1049–57.
5. Ehrenthal D, Haeger L, Griffin T, Compton C. Familial pancreatic adenocarcinoma in three generations. A case report and a review of the literature. Cancer 1987;59:1661–4.
6. Ghadirian P, Simard A, Baillargeon J. Cancer of the pancreas in two brothers and one sister. Int J Pancreatol 1987;2:383–91.
7. Dat NM, Sontag SJ. Pancreatic carcinoma in brothers. Ann Intern Med 1982; 97:282.
8. MacDermott RP, Kramer P. Adenocarcinoma of the pancreas in four siblings. Gastroenterology 1973;65:137–9.
9. Friedman JM, Fialkow PJ. Familial carcinoma of the pancreas. Clin Genet 1976;9:463–9.
10. Ghadirian P, Boyle P, Simard A, et al. Reported family aggregation of pancreatic cancer within a population-based case-control study in the Francophone community in Montreal, Canada. Int J Pancreatol 1991;10: 183–96.
11. Fernandez E, La Vecchia C, D'Avanzo B, et al. Family history and the risk of liver, gallbladder, and pancreatic cancer. Cancer Epidemiol Biomarkers Prev 1994;3:209–12.
12. Falk RT, Pickle LW, Fontham ET, et al. Life-style risk factors for pancreatic cancer in Louisiana: a case-control study. Am J Epidemiol 1988;128:324–36.
13. Silverman DT, Schiffman M, Everhart J, et al. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. Br J Cancer 1999;80:1830–7.
14. Schenk M, Schwartz AG, O'Neal E, et al. Familial risk of pancreatic cancer. J Natl Cancer Inst 2001;93:640–4.
15. McWilliams RR, Rabe KG, Olswold C, et al. Risk of malignancy in first-degree relatives of pancreatic cancer patients. Cancer 2005;104:388–94.
16. Amundadottir LT, Thorvaldsson S, Gudbjartsson DF, et al. Cancer as a complex phenotype: pattern of cancer distribution within and beyond the nuclear family. PLoS Med 2004;1:e65.
17. Coughlin SS, Calle EE, Patel AV, Thun MJ. Predictors of pancreatic cancer mortality among a large cohort of United States adults. Cancer Causes Control 2000;11:915–23.
18. Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res 2004;64:2634–8.
19. Hruban RH, Petersen GM, Ha PK, Kern SE. Genetics of pancreatic cancer. From genes to families. Surg Oncol Clin N Am 1998;7:1–23.
20. Lynch HT, Smyrk T, Kern SE, et al. Familial pancreatic cancer: a review. Semin Oncol 1996;23:251–75.
21. Lal G, Liu G, Schmocker B, et al. Inherited predisposition to pancreatic adenocarcinoma: role of family history and germ-line p16, BRCA1, and BRCA2 mutations. Cancer Res 2000;60:409–16.
22. Murphy KM, Brune KA, Griffin C, et al. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%. Cancer Res 2002;62:3789–93.
23. Hahn SA, Greenhalf B, Ellis I, et al. BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst 2003;95:214–21.
24. Rogers CD, van der Heijden MS, Brune K, et al. The genetics of FANCC and FANCG in familial pancreatic cancer. Cancer Biol Ther 2004;3:167–9.
25. Rogers CD, Couch FJ, Brune K, et al. Genetics of the FANCA gene in familial pancreatic cancer. J Med Genet 2004;41:el26.
26. Eberle MA, Pfutzger R, Pogue-Geile KL, et al. A new susceptibility locus for autosomal dominant pancreatic cancer maps to chromosome 4q32–34. Am J Hum Genet 2002;70:1044–8.
27. Klein AP, Beaty TH, Bailey-Wilson JE, et al. Evidence for a major gene influencing risk of pancreatic cancer. Genet Epidemiol 2002;23:133–49.
28. Rulyak SJ, Lowenfels AB, Maisonneuve P, Brentnall TA. Risk factors for the development of pancreatic cancer in familial pancreatic cancer kindreds. Gastroenterology 2003;124:1292–9.
29. James TA, Sheldon DG, Rajput A, et al. Risk factors associated with earlier age of onset in familial pancreatic carcinoma. Cancer 2004;101:2722–6.
30. Bailey-Wilson JE, Amos CI, Pinney SM, et al. A major lung cancer susceptibility locus maps to chromosome 6q23–25. Am J Hum Genet 2004;75:460–74.
31. Center for Inherited Disease Research [homepage on the Internet]. Genotyping services [updated 2006 Jan 6; cited 2006 Jan 12]. Available from: http://www.cidr.jhmi.edu/index.html.
32. WHO. International classification of diseases for oncology. Imprint. Geneva: WHO; 1976.
33. National Cancer Institute [homepage on the Internet]. U S. National Institutes of Health. Certificates of confidentiality [updated 2005 Jan 1; cited 2006 Jan 12]. Available at: http://www.cancer.gov/clinicaltrials/conducting/certificates-of-confidentiality.
34. Weeks DE, Ott J, Lathrop GM. SLINK: a general simulation program for linkage analysis [abstract]. Am J Hum Genet 1990;47:A204.
35. Goggins M, Hruban RH, Kern SE. BRCA2 is inactivated late in the development of pancreatic intraepithelial neoplasia: evidence and implications. Am J Pathol 2000;156:1767–71.
36. Rosty C, Ueki T, Argani P, et al. Overexpression of S100A4 in pancreatic ductal adenocarcinomas associated with poor differentiation and DNA hypomethylation. Am J Pathol 2002;160:45–50.
37. National Cancer Institute [homepage on the Internet]. Surveillance Epidemiology and End Results (SEER) Program. SEER*Stat Database: Incidence - SEER 13 Regs Public-Use, Nov 2004 Sub (1973–2002 varying), National Cancer Institute DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission [cited 2006 Jan 12]. Available from: http://www.seer.cancer.gov.
38. National Cancer Institute [homepage on the Internet]. Surveillance Research Program, National Cancer Institute SEER*Stat software version 6.1.4 [cited 2006 Jan 12]. Available from: http://www.seer.cancer.gov/seerstat.
39. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
40. King MC, Marks JH, Mandell JB. New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003;302:643–6.
41. Voskuil DW, Vasen HF, Kampman E, van't Veer P. Colorectal cancer risk in HNPCC families: development during lifetime and in successive generations. National Collaborative Group on HNPCC. Int J Cancer 1997; 72:205–9.
42. Bermejo J, Hemminki K. Risk of cancer at sites other than the breast in Swedish families eligible for BRCA1 or BRCA2 mutation testing. Ann Oncol 2004;15:1834–41.
43. Lynch HT, Fusaro RM. Pancreatic cancer and the familial atypical multiple mole melanoma (FAMMM) syndrome. Pancreas 1991;6:127–31.
44. Goldstein AM, Fraser MC, Struewing JP, et al. Increased risk of pancreatic cancer in melanoma-prone kindreds with $p16^{INK4}$ mutations. N Engl J Med 1995;333:970–4.
45. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 2000;119:1447–53.
46. van der Heijden MS, Yeo CJ, Hruban RH, Kern SE. Fanconi anemia gene mutations in young-onset pancreatic cancer. Cancer Res 2003;63:2585–8.
47. Couch FJ, Johnson MR, Rabe K, et al. Germ line Fanconi anemia complementation group C mutations and pancreatic cancer. Cancer Res 2005;65:383–6.
48. Whitcomb DC, Gorry MC, Preston RA, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet 1996;14: 141–5.
49. Whitcomb DC, Preston RA, Aston CE, et al. A gene for hereditary pancreatitis maps to chromosome 7q35. Gastroenterology 1996;110:1975–80.
50. Lynch HT, Voorhees GJ, Lanspa SJ, et al. Pancreatic carcinoma and hereditary nonpolyposis colorectal cancer: a family study. Br J Cancer 1985;52:271–3.
51. McWilliams R, Highsmith WE, Rabe KG, et al. Cystic fibrosis transmembrane regulator gene carrier status is a risk factor for young onset pancreatic adenocarcinoma. Gut 2005;54:1661–2.

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*Cancer Epidemiol Biomarkers Prev* 2006;15:704-710.