Published in final edited form as:
J Surg Oncol. 2013 January ; 107(1): 1–7. doi:10.1002/jso.23149.

Epidemiology of Pancreatic Cancer and the Role of Family History

Sara H. Olson, PhD[1,*] and **Robert C. Kurtz, MD**[2]

[1]Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York

[2]Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York

Abstract

Pancreatic cancer is a lethal disease for which only a small number of risk factors have been identified. In addition to older age, male gender, and black race, risk factors include smoking, obesity, long-standing diabetes and pancreatitis, and heavy alcohol use; allergies such as hay fever are related to lowered risk. Several genetic syndromes increase risk of pancreatic cancer. Work on more common genetic variants promises to reveal more potentially important genetic associations.

Keywords

epidemiology; smoking; obesity; diabetes; allergies; genetic syndromes

Incidence and Mortality

In the USA, nearly 44,000 new cases of pancreatic cancer are expected in 2012 [1]; the age-adjusted incidence rate in 2008 was 12.0 per 100,000, reflecting a slight but statistically significant increase in the 2000–2008 period [2]. Mortality is almost as high as incidence, 10.9 per 100,000 [3], with more than 37,000 deaths expected in 2012 [1]. In the USA, pancreatic cancer ranks fourth in causes of death from cancer. In other developed countries, incidence rates are similar to those in the USA, while they are considerably lower in less developed countries: With the world age distribution used for standardization, age-adjusted rates are 7.0 per 100,000 in the USA, 6.7 in other developed countries, and 2.4 in less developed countries (Fig. 1, [4]).

Risk Factors for Pancreatic Cancer

Age, Gender, and Race

The strongest risk factor for pancreatic cancer is increasing age. In the USA, the median age at diagnosis is 72 [2]; no other cancer has a higher median age. Risk is low (10.4 per 100,000) in those aged 50–54, increasing sharply to 73.5 per 100,000 in those aged 75–79

[*]Correspondence to: Sara H. Olson, PhD, Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY. Fax: 646 735 0010. olsons@mskcc.org.

[3] and continuing to increase in older individuals (Fig. 2). Risk is higher in men (13.5 per 100,000) than in women (10.8 per 100,000) (Fig. 3); the difference between men and women probably reflects smoking habits. Risk is considerably higher in blacks than in non-Hispanic whites in the USA (15.8 vs. 12.0 per 100,000) and somewhat lower in Asians (9.5 per 100,000) and Hispanics (10.7 per 100,000) [3]. Because of different age distributions in the USA for racial and ethnic groups, the actual number of minority patients, including blacks, with pancreatic cancer is quite small [5], making it difficult to study risk factors or outcomes separately in subgroups. Examination of possible reasons for the racial discrepancy in incidence indicated that reasons differed for men and women, but that most of the difference between blacks and whites were explained by established or suspected risk factors [6].

Smoking

Cigarette smoking is the strongest environmental risk factor. A recent meta-analysis of 82 studies, including both case-control and cohort designs, reported a 75% increased risk of pancreatic cancer in current smokers (OR = 1.74, 95% CI 1.61–1.87) [7]. The same result was found in a pooled analysis of 13 studies, including 12 cohorts [8] while somewhat higher risk was found in an analysis of 12 case-control studies, with a more than twofold increase in risk for current smokers [9]. Results from case-control studies are more likely than those from cohort studies to reflect smoking status at the time of diagnosis, since smoking cessation reduces risk and those who smoked at baseline in cohort studies may have quit at a later time. Studies have shown varying results with respect to the length of time required after smoking cessation for risk to match that of those who have never smoked, with most studies finding periods of 10 [7,10] to 15 or more years [8,9] required. Passive smoking (environmental tobacco smoke) among those who have never smoked appears to have little influence on risk [10,11], although some studies have noted a positive association [12].

Obesity

The association between overweight and obesity and pancreatic cancer was highlighted in the landmark 2003 study from the American Cancer Society's prospective Cancer Prevention Study II on overweight and obesity and risk of death from cancer [13]. With 16 years of follow-up, during which 3,358 deaths due to pancreatic cancer were identified in cohort members, risks increased steadily for both men and women as baseline body mass index (BMI) increased above the normal range. In men, death due to pancreatic cancer was 50% higher among those with class II obesity (BMI ≥35). Among women, risk was strongly increased among those with class III obesity (BMI >40): RR = 2.76, 95% CI 1.74-4.36). A more recent analysis, with 2,135 cases pooled from 14 cohort studies [14], supported these findings, with the obese 47% more likely to be diagnosed with pancreatic cancer. Weight gain between early adulthood and cohort entry was also related to increased risk. An association with weight in early adulthood was also reported in a large case-control study [15]. From pooled analyses of data from cohort studies, there is some evidence that central adiposity is also associated with greater risk [14,16]. Some large studies and pooled analyses have suggested that risk associated with high BMI is stronger in non-smokers [13,14,16,17], but other studies have not found this relationship [15]. Although physical activity is related

to obesity, the literature on association of physical activity with risk of pancreatic cancer is heterogeneous and there is no clear association [18].

Diabetes

While an association between presence of diabetes and risk of pancreatic cancer is a consistent finding in epidemiologic studies, the results differ markedly according to the length of time between diagnosis of diabetes and diagnosis of pancreatic cancer, with the highest association for diabetes diagnosed close to the time of cancer diagnosis, and only moderately increased risk with longer duration of diabetes. Two recent meta-analyses, one including 35 cohort studies [19] and the other including 19 cohort and 17 case-control studies [20] observed an increased risk of almost 2 overall (RR = 1.94, 95% CI 1.66-2.27; RR = 1.82 (95% CI 1.66-1.99, respectively). In both analyses, for those studies that evaluated risk according to the timing of diabetes and cancer, risk was increased about 50% for those with diabetes diagnosed ≥10 years earlier. Similar results were found in a pooled analysis of three large case-control studies [21], with threefold increased risk for diabetes diagnosed within 2 years before cancer diagnosis, and 30-40% increased risk for long-term diabetes (>10 years). Although the association between diabetes and pancreatic cancer could be confounded by the effects of high BMI and smoking, this does not appear to explain the results [19,21]. The relatively high-risk estimates for diabetes diagnosed close to the time of cancer diagnosis is likely to represent reverse causality, with cancer-related alterations to pancreatic function leading to diabetes. A study in the Mayo clinic population showed an increase in prospectively measured plasma glucose beginning 24 months before diagnosis [22], indicating that new-onset diabetes is likely to be caused by the tumor and could potentially be a means of identifying early disease. A small number of studies have reported that use of metformin in those with diabetes is related to reduced risk of pancreatic cancer [23-25]; the most recent study [25] found the effect only among women, for reasons that are unclear.

Pancreatitis

Pancreatitis is both an established risk factor for pancreatic cancer and an early indicator of the presence of cancer. Studies that have investigated the timing of pancreatitis relative to that of cancer have found that risk is highest in the year before cancer diagnosis, suggesting that the cancer may be initially diagnosed as pancreatitis. At the same time, studies that have investigated risk with many years between diagnoses have also found that risk is increased [26]. Increased risk for long-term disease has also been found in retrospective cohorts of individuals with pancreatitis [27-29]. In spite of this association, the prevalence of pancreatitis in the population is very low, making it unlikely to that many cases of pancreatic cancer are attributable to this condition. Hereditary pancreatitis attributable to known genetic mutations is discussed below in the section on family history.

Alcohol

Light and moderate consumption of alcohol has not been found to be related to increased risk of pancreatic cancer, while heavy consumption is likely to increase risk [30]. Pooled analyses of 10 case-control studies and 14 cohort studies resulted in ORs of 1.5 (95% CI 1.2-1.8) for consumption of ≥6 drinks per day (≥84 g per day) [31] and 1.22 (95% CI

1.03-1.45) for consumption of ≥30 g of alcohol per day [32], respectively. Alcohol consumption is associated with cigarette smoking; in addition, heavy alcohol consumption is a common cause of pancreatitis, possibly making it difficult to disentangle the effects of these exposures on risk.

Allergies

A number of epidemiologic studies have investigated associations between self-reported allergies and various types of cancer [33,34]; reduced risk for pancreatic cancer is among the most consistent findings. A meta-analysis of 14 pancreatic cancer studies showed a 30% reduced risk in those with any allergies and a 45% reduced risk in those with respiratory allergies such as hay fever in studies with direct interviews rather than proxies [35]. Since the publication of the meta-analysis, three new case-control studies [36-38], one expanded case-control study [39], and a cohort study [40] have supported these results. A recent review of 11 published studies that reported on risks associated with any allergy [26] found statistically significantly reduced risk in most of the studies, and consistently reduced risk in those with respiratory allergies such as hay fever and allergies to plants or pollen. Other allergies, such as those to foods and medications, have been less well studied and associations with risk are unclear. Although asthma is often found in conjunction with respiratory allergies, it is not consistently associated with risk and several studies have shown no association [26,35].

In contrast, studies conducted in Sweden [41,42] and the USA [43] in cohorts of people with allergies have not found evidence that self-reported allergies, skin prick tests, or IgE levels were associated with decreased risk of cancer overall or with specific cancers, including pancreatic cancer. Results from these cohort studies remain inconclusive because the patients studied were young and follow up was only for up to 13 years, resulting in only a handful of cases; in addition, data were not always available to adjust for potential confounding factors such as smoking.

Genetic Polymorphisms

Several known genetic mutations leading to inherited susceptibility to pancreatic cancer are discussed in the section below on family history. In addition to these established factors that confer high risk but are rare in the population, recent genome-wide association studies (GWAS) have been successful in identifying more common germline variants that are related to risk of pancreatic cancer. In the first of the PanScan studies conducted by the National Cancer Institute with DNA from several cohort and case-control studies [44], the strongest association was with variants that determine ABO blood type. Increased risk for non-O blood types had been noted in earlier studies [45,46], and recent work based on genotypes has confirmed that risk increases with each non-O allele: Risk is higher for the AA genotype than for AO, and higher for BB than for BO [47]. An interaction between ABO blood type and presence of *H pylori* [48] has been reported; there have been mixed results among studies that have investigated *H pylori* and risk, but the weight of evidence is that this exposure is related to increased risk [49].

GWAS studies in Caucasian [44,50] and Asian populations [51,52] also identified several loci at or near genes that had not previously been implicated in pancreatic cancer risk. A study using a pleiotropy approach, including only SNPs previously found to be associated with other cancers or diseases, identified risk associated with *HNF1A*, a gene related to diabetes and other traits [53]. The influence of genetic variants on risk of pancreatic cancer is an area of active research, with ongoing studies including pathways analyses and functional studies as well as new GWAS.

Family History and Pancreatic Cancer Risk

For several decades the inherited susceptibility to pancreatic cancer has been described in multiple case reports. Clustering of pancreatic cancer in families is illustrated by an early report of the occurrence of pancreatic cancer in three women in successive generations who, over 11 years, developed pancreatic cancer each at a younger age [54]. The authors speculated that inheritance may play a role in some pancreatic cancers. In 1985 Lynch et al. [55] originally described five generations of a family with early age of onset of multiple right-sided colon cancers and pancreatic cancer. The occurrence of pancreatic cancer in the family was felt to be “enigmatic.” This family was felt to represent hereditary non-polyposis colon cancer and this report was an early description of what we now believe to be a specific genetic susceptibility to pancreatic cancer.

Familial Pancreatic Cancer

It is now felt that two broad categories of hereditary risk for pancreatic cancer can be defined. Familial pancreatic cancer is defined as an inherited predisposition based on family clustering in families in which there are multiple first and second degree relatives with ductal pancreatic adenocarcinoma in the absence of a known genetic susceptibility syndrome. A family history of pancreatic cancer is seen in between 5–10% of individuals with pancreatic cancer [56]. As pancreatic cancer is a relatively common cancer, more than one family member may be affected solely by chance alone. There also may be common environmental factors, such as smoking or high BMI, or indeed, an as yet unidentified common genetic factor. Having multiple family members with pancreatic cancer increases the risk of non-affected family members developing the disease. This is especially true when multiple first-degree relatives have pancreatic cancer. When two or more first-degree relatives are affected, one study showed the odds ratio to be 4.26 (95% CI = 0.48–37.79) [57]. Scientists at Johns Hopkins using their National Familial Pancreas Tumor Registry found that when at least one pair of first degree relatives were affected with pancreatic cancer, the risk of developing pancreatic cancer was 18 times that for relatives of an individual with only one sporadic pancreatic cancer. In those pancreatic cancer kindreds with three or more affected family members there was a 57-fold (95% CI = 12.4–175) increased risk of pancreatic cancer [58]. It has become clear that in these familial pancreatic cancer families, the risk of developing pancreatic cancer is closely tied to the number of first-degree relatives in the family with the disease.

Germline Mutations and Pancreatic Cancer

Pancreatic cancer also occurs in the setting of well defined cancer syndromes, so-called cancer susceptibility syndromes, where an identifiable germline mutation may lead to the development of pancreatic adenocarcinoma.

BRCA 1 and BRCA2

Perhaps one of the most well known of the cancer predisposition syndromes is the Hereditary Breast and Ovarian Cancer Syndrome. Women who carry gene mutations of the tumor suppressor genes, *BRCA1* or *BRCA2*, have very high lifetime risks for breast and ovarian cancers. The risk of cancers other than breast and ovarian cancer was investigated by a consortium of 20 centers in Europe and North America, in which 173 breast-ovarian cancer families with *BRCA2* mutations were identified. Several cancers were found to have a statistically significant increased risk. These included prostate, gallbladder, bile duct, stomach, and pancreas. For pancreatic cancer the relative risk was 3.51 (95% CI = 1. 87–6.58) [59]. Using direct sequencing of constitutional DNA, Murphy et al. [60] analyzed samples from patients with pancreatic cancer who were enrolled in their Familial Pancreatic Tumor Registry for mutations in four tumor suppressor candidate genes including *BRCA2*. Samples were taken from families in which three or more family members were affected with pancreatic cancer, and at least two were first-degree relatives. *BRCA2* gene sequencing identified five mutations believed to be deleterious (17.2%). Three patients harbored the 6174delT frameshift mutation. These findings confirm the increased risk of pancreatic cancer in individuals with *BRCA2* mutations. The authors also concluded that germline *BRCA2* mutations are the most common inherited genetic alteration in familial pancreatic cancer. In a study by Lynch et al. [61], pancreatic cancer was seen in nine of 15 families where the *BRCA1* mutation was either confirmed or inferred. Thompson et al. [62] analyzed data on 11,847 individuals from 699 families. The overall increased risk of cancer in those with deleterious *BRCA1* mutations at sites other than breast and ovary is small. *BRCA1* mutations may confer increased risks of other abdominal cancers in women and increased risks of pancreatic cancer in men and women.

PALB2

Rahman et al. [63] demonstrated that truncating mutations in *PALB2* (partner and localizer of *BRCA2*) in individuals with familial breast cancer confer a 2.3-fold higher risk of the disease [64]. The group at Johns Hopkins identified such a mutation in a patient with familial pancreatic cancer and found an additional three patients with pancreatic cancer and *PALB2* mutations in 96 studied [65].

Lynch Syndrome—Hereditary Nonpolyposis Colon Cancer (HNPCC)

Lynch syndrome is an autosomal dominant condition caused by mutations in the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and PMS2. Colorectal and endometrial cancers are the most commonly described cancers in this syndrome [66]. Studies of the risk of pancreatic carcinoma in Lynch syndrome patients when compared to the general population have produced variable results. Pancreatic cancer has been included as an HNPCC-associated tumor in the revised Bethesda guidelines [67]. Geary et al. [68] reviewed the family histories

of 130 individuals with documented mismatch repair gene mutations. They found 22 cases of pancreatic cancer; half were in proven or obligate carriers. The risk as defined by their study was about seven times expected. Young age of onset was also characteristic, with 14 of 20 with a known age being under the age of 60. Kastrinos et al. [69] found 31 out of 147 families with mismatch repair gene mutations where there was at least one reported case of pancreatic cancer. The cumulative risk of pancreatic cancer in their families with gene mutations was calculated to be 1.31% (0.31–2.32%) in young individuals up to age 50. This rose to 3.68% (1.45–5.88%) up to age 70, an 8.6-fold increase over the general population. It has been suggested that pancreatic cancer occurring in individuals with Lynch Syndrome may have a somewhat better prognosis. Yamamoto et al. [70] described three Lynch syndrome patients with high levels of microsatellite instability in their pancreatic cancers. These individuals had a significantly longer overall survival than pancreatic cancer patients with low tumor levels of microsatellite instability or patients with microsatellite stable tumors.

Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)

The familial atypical multiple mole melanoma syndrome is caused by a germline mutation in the tumor suppressor gene *CDKN2A* (*p16*) on chromosome 9. Mutations in *CDKN2A* occur in about 20% of familial melanoma families in North America, Asia, Australia, and Europe [71]. Several studies have demonstrated an increased risk of pancreatic cancer among *CDKN2A* melanoma-prone families [72,73]. In the Dutch FAMMM registry, pancreatic cancer was found to be the second most common cancer in mutation carriers after melanoma [74]. Vasen et al. [75] reported on a surveillance program for individuals with germline mutations of p16-Leiden. It is estimated that carriers of the mutated gene have a lifetime risk of 15–20% of developing pancreatic cancer. Using MRI and MRCP as the surveillance tools, approximately 9% of the 79 people studied were found to have developed pancreatic cancer.

Peutz–Jeghers Syndrome

Peutz–Jeghers syndrome is an autosomal dominant disease characterized by hamartomatous polyps of the gastrointestinal tract and by mucocutaneous melanin deposits and caused by germline mutations of *STK11* (serine threonine kinase 11). These mutations can be found in the majority (66–94%) of Peutz–Jeghers syndrome patients [76]. In 1987, Giardiello et al. [77] described the increased risk of cancer in patients with Peutz–Jeghers syndrome. Relative-risk analysis demonstrated that the development of cancer in Peutz–Jeghers syndrome patients was 18 times greater than expected in the general population, and the cumulative lifetime risk for pancreatic cancer from age 15 to 64 was 36%. Ninety-six cancers were found in a study of 419 individuals with Peutz–Jeghers syndrome of which 297 had documented *STK11/LKB1* mutations. The most frequent cancers represented in this analysis were gastroesophageal, small bowel, colorectal, and pancreatic. Hearle et al. [78] found 96 cancers in 297 individuals with Peutz–Jeghers syndrome with germline mutations in *STK11/LKB1*. Here again, multiple sites of gastrointestinal cancers were seen which included pancreatic cancer. The issue of ascertainment bias inflating the overall cancer risk was raised by Giardeillo et al. [76].

Familial Adenomatous Polyposis (FAP)

Familial adenomatous polyposis is an autosomal dominantly inherited disorder caused by germline mutation of the adenomatous polyposis coli (APC) gene on chromosome 5q. While colorectal cancer is the major cancer risk in affected individuals, the relative risk of other cancers such as thyroid and pancreas has also been described [79]. A study using the Johns Hopkins Polyposis registry found four patients with pancreatic cancer in their cohort of 1,391 patients with FAP. Patients with FAP are now surviving longer due to early identification and management of their colorectal cancer risk; as a result, more frequent diagnoses of extracolonic cancers, such as pancreatic cancer can be expected [80].

Hereditary Pancreatitis

Hereditary pancreatitis is an autosomal dominant disease. Acute pancreatitis begins early and can lead to chronic pancreatitis. The disease has variable expression and penetrance is estimated to be about 80% [81]. In 1996, Whitcomb et al. [82] reported that an arginine–histidine substitution at residue 117 of the cationic trypsinogen gene was likely the cause of hereditary pancreatitis. The gene for hereditary pancreatitis was found to map to chromosome 7q35 [83]. Chronic pancreatitis has been linked to pancreatic cancer, and an international multi-institutional study estimated the risk of pancreatic cancer in affected individuals in hereditary pancreatitis cohorts to be about 40% by age 70 [81].

Management of Individuals With Pancreatic Cancer Risk Due to Family History

Management of high-risk individuals from pancreatic cancer families remains an important issue. A number of familial pancreatic cancer registries have been developed throughout the United States and the world [84]. Screening programs attempting to identify these pancreatic lesions in at-risk healthy family members are underway and several have begun to report their preliminary findings. Canto et al. [85] at Johns Hopkins, utilizing endoscopic ultrasound and endoscopic retrograde cholangiopancreatography (ERCP), initially reported diagnostic yield of 5.3% in a pilot study of 38 patients. One invasive cancer was detected. In a second report from [86], seven high-risk individuals were identified with pathologically confirmed intraductal papillary mucinous neoplasms (IPMNs) and one patient had a pancreatic intraepithelial neoplasm (PanIN) for a diagnostic yield of 10%. In a similar screening program in our Memorial Sloan-Kettering Cancer Center Familial Pancreatic Tumor Registry, utilizing cross-sectional imaging (magnetic resonance cholangiopancreatography (MRCP) and CT), we found IMPNs in eight of 113 healthy at-risk individuals [87]. Langer et al. [88] recently published their results of screening 76 individuals from 34 familial pancreatic cancer families culled from the German National Collection for Familial Pancreatic Cancer. Ten individuals were found to have solitary pancreatic lesions and seven of these underwent surgery. No cancers were identified and only one IPMN was found for a low diagnostic yield of 1.3%.

Recommendations of the Fourth International Symposium of Inherited Diseases of the Pancreas are that screening of familial pancreatic cancer family members is appropriate in the context of a clinical trial [89]. Their recommendation is for screening of healthy individuals with at least three affected first degree relatives and in those individuals with a known BRCA2 mutation and at least one family member with pancreatic cancer. The age

when screening should begin is at age 50 or 10 years younger than the youngest affected family member. The frequency of screening remains an unanswered question, but genetic counseling is strongly recommended.

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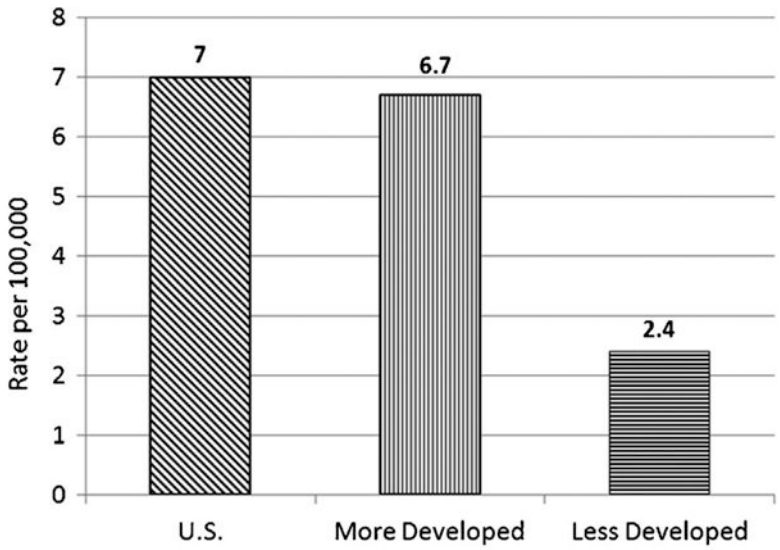

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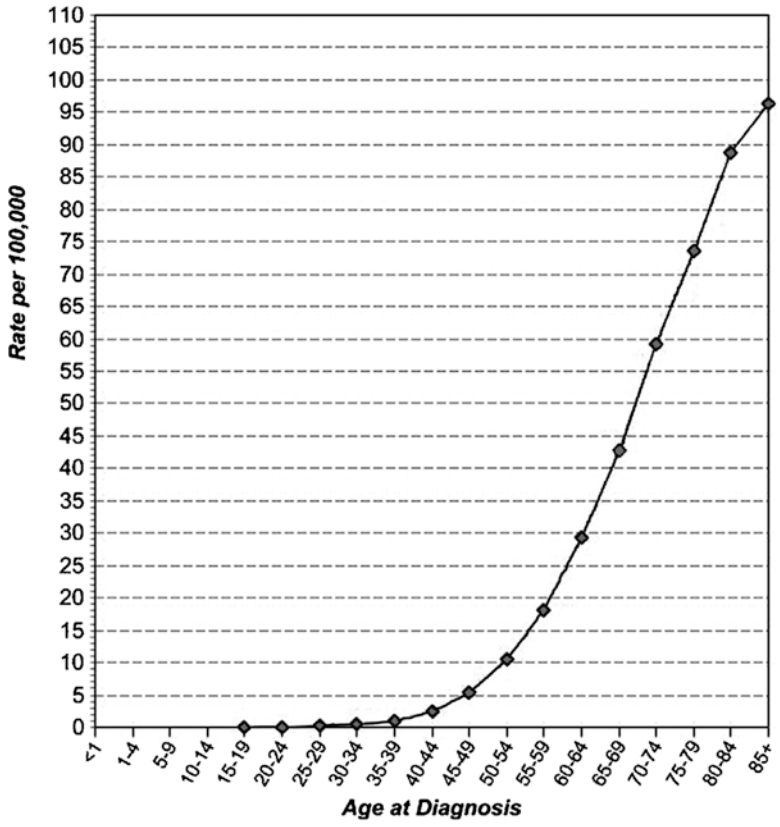

Fig. 2.

Age-Specific (Crude) SEER Incidence Rates By Cancer Site, All Ages, All Races, Both Sexes, 2000-2008 (SEER 17). Fast Stats: An interactive tool for access to SEER cancer statistics. Surveillance Research Program, National Cancer Institute. http://seer.cancer.gov/faststats. (Accessed on 4-10-2012).

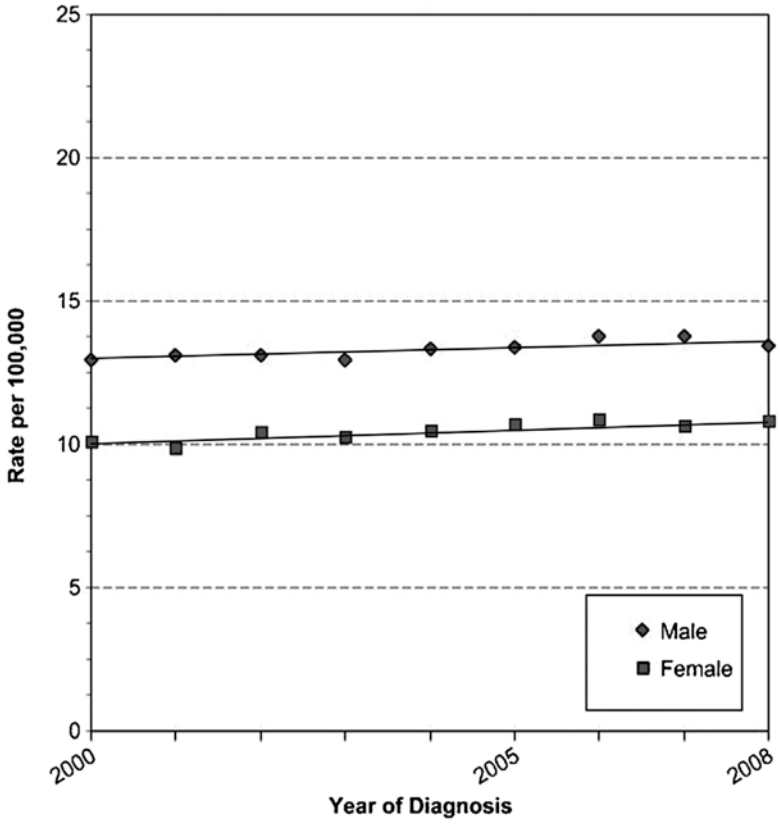

Fig. 3.

Age-Adjusted SEER Incidence Rates By Sex, Pancreas, All Ages, All Races, 2000-2008 (SEER 17). Fast Stats: An interactive tool for access to SEER cancer statistics. Surveillance Research Program, National Cancer Institute; http://seer.cancer.gov/faststats. (Accessed on 4-10-2012).