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PROSPECTS

Risk Factors for Pancreatic Cancer

Albert B. Lowenfels[1]* and Patrick Maisonneuve[2]

[1]Department of Surgery, New York Medical College, Valhalla, New York
[2]European Institute of Oncology, Milan, Italy

Abstract In the United States, the cumulative mortality or lifetime risk of dying from pancreatic cancer is about 1–2%, but although this form of cancer is rare, nearly all patients die from the disease within one to two years. Because of its lethality, pancreatic cancer now ranks fourth as a cause of death from cancer. There are country-specific differences in rates, perhaps explained by differences in life-style factors or diet. African-Americans in the USA have rates that are about 50% higher than Caucasians. Smoking is the major known risk factor for this cancer, explaining 20–30% of all cases. Another 5–10% of causes are caused by germline mutations, with mutations in BRCA2 being the most frequent. Two background diseases increase the risk of pancreatic cancer—pancreatitis, and diabetes. Major challenges presented by this cancer are: 1) determination of the molecular pathways that make this cancer so aggressive; 2) development of new modalities, perhaps based on proteomics, to enhance early detection. J. Cell. Biochem. 95: 649–656, 2005.

Key words: pancreas; cancer; risk factors; epidemiology

Pancreatic cancer is a rare human tumor with age-adjusted rates in most countries ranging from about 5 to 10 new cases per 100,000 persons per year. Despite its relative scarcity, this tumor has attracted increasing interest because the mortality rate is nearly 100%. Most patients who are diagnosed with this tumor die within a year and the 5 year survival is less than 5%. Only a very few tumors are as aggressive as pancreatic cancer and unlike many other cancers, discovery of a small tumor does not always lead to improved survival.

The anatomy of the pancreas leads to another challenge. The gland is situated in the most inaccessible part of the abdomen, making it unreachable by any conventional endoscopic approach. Because of its location, effective screening procedures have yet to be devised. Furthermore, the proximity to major digestive organs such as the bile ducts, and vital vascular structures, greatly complicates surgical therapy. Moreover, pancreatic cancer cells appear to be especially resistant to both chemotherapy and radiotherapy.

All of these factors make pancreatic cancer one of our greatest oncologic challenges.

DEVELOPMENT OF PANCREATIC CANCER

Most digestive tract tumors are known to develop gradually, slowly progressing from a normal to a malignant cell type, often having several stages with gradually increasing cellular distortion. The progression of colon tumors from colonic polyps to cancer is an excellent example.

Careful examination of resected pancreata reveals evidence of premalignant changes called PANINS that gradually become more severe as pancreatic cancer develops [Hruban et al., 2001]. As these lesions become more aggressive, mutations accumulate, with K-ras changes appearing as an early change [Hruban et al., 1993].

Until recently, there have been only limited animal models to study the experimental development of pancreatic cancer. The Syrian hamster when exposed to the potent carcinogen *N*-nitrosobis-(2-oxopropyl) amine (BOP) develops pancreatic, but it has been difficult to study the progression of the normal to the

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*Correspondence to: Albert B. Lowenfels, MD, Professor of Surgery, Department of Surgery, New York Medical College, Valhalla, NY 10595. E-mail: Lowenfel@nymc.edu

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malignant pancreas gland in this model. Recently Hingorani et al. [2003] have developed a mouse model for pancreatic cancer by directing endogenous expression of K-ras(G12D) to progenitor cells of the mouse pancreas. This model produces changes in the mouse pancreas that mimic the progressive PANIN stages that are found in the human pancreas. Eventually these animals develop pancreas cancer. The availability of this valuable new experimental model should help advance the study of human pancreatic cancer [Hingorani et al., 2003].

DESCRIPTIVE EPIDEMIOLOGY

In the United States pancreas cancer develops in approximately 30,000 patients per year, with about the same number expected annually in Europe, and about 20,000 annual cases in Japan [Lowenfels and Maisonneuve, 2004]. Compared with more common tumors such as lung, breast, colon, or prostate tumors, pancreas cancer is a rare, "orphan" cancer: however, because it is so lethal, it ranks fourth a cause of death from cancer. With the rapid advancement of effective screening and therapeutic regimes for breast and colon cancer resulting in decreased deaths from these diseases, pancreas cancer is likely to become an increasingly frequent cause of death from cancer.

Pancreatic cancer has an uneven world distribution (Fig. 1). At present, perhaps related to smoking or the inability to detoxify tobacco-related carcinogens, pancreas cancer rates are higher in African-Americans (in the USA) populations than in most other cancer registries. In general, high rates are found in developed, industrialized countries; lower rates occur in developing regions of the world.

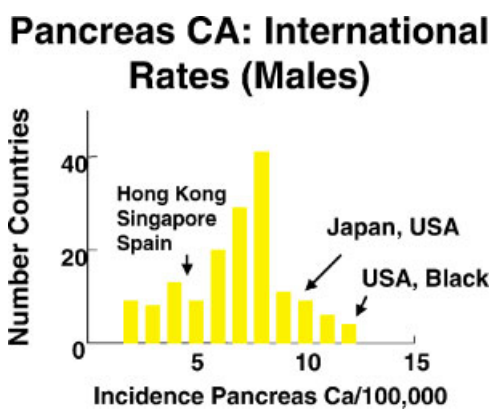

Fig. 1. Histogram demonstrating wide international variation in the incidence of pancreatic cancer. From reference [Lowenfels and Maisonneuve, 2004]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

There are well-recognized racial factors affecting the frequency of pancreatic cancer that may originate at the molecular level. Chinese pancreatic cancer patients may have different K-ras and p53 expressions than other populations [Dong et al., 2000]. The molecular pattern of K-ras mutations in African-Americans (in the USA) may be different than in other populations. Also, there may be racial differences in survival patterns after diagnosis of pancreatic cancer, perhaps related to racial differences in aggressiveness of tumor type [Longnecker et al., 2000].

Incidence rates for pancreatic cancer have changed considerably over time. In most countries, rates have increased over the past several decades as a predictable response to increases in smoking prevalence. It is encouraging to note that in a few populations, such as USA males, where smoking rates have declined, there has been a slight but measurable decrease in the frequency of pancreatic cancer (Fig. 2).

Age is one of the main factors related to pancreas as well as other cancers, so as people live longer, we can anticipate a measurable increase in pancreatic cancer.

ENVIRONMENTAL AND LIFESTYLE FACTORS

Pancreatic cancer has been linked to smoking and is unquestionably one of the major smoking-related tumors. Unlike the lung, where tobacco smoke and tobacco degradation products are in direct contact with pulmonary tissue, the pancreas is exposed to tobacco products indirectly. Tobacco-related carcinogens reach the pancreas either via the blood stream, or perhaps through exposure of the pancreas to either duodenal contents or to bile. Most pancreatic cancers occur in the head of the gland and this region is where exposure to tobacco carcinogens contained in the duodenal juice or bile could occur.

Since exposure to tobacco products is lower in the pancreas than in the lung, it is understandable that the smoking-related risk of pancreatic cancer is not as high as that of lung cancer. Most studies have found that smoking results in about a twofold increased risk of pancreas cancer, in contrast to the 10–15 fold

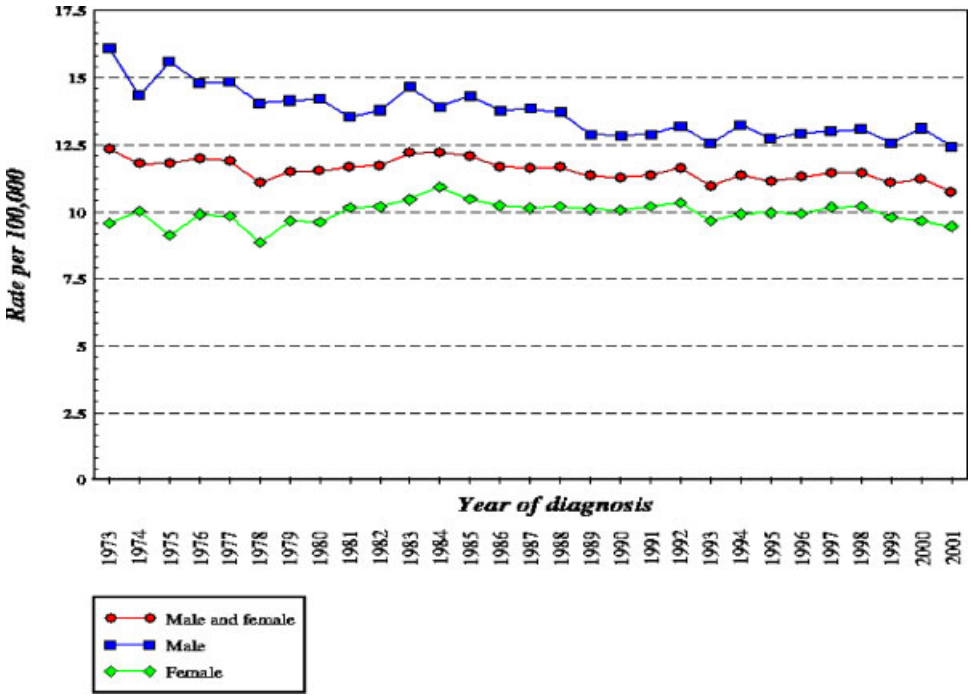

Fig. 2. Time trends for incidence of pancreatic cancer in the United States 1973–2001 for males, females, and both sexes combined [Time trends for pancreatic cancer in the USA, 2003]. There has been a modest decrease in rates for males; female rates are unchanged. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

smoking-related risk of lung cancer [Boyle et al., 1996; Engeland et al., 1996]. Most studies confirm the anticipated finding of a dose response, with higher rates of pancreas cancer being linked to heavier smoking exposure. In a 40-year follow-up study of British physicians, Richard Doll found that pancreatic cancer rates in non-smokers, ex-smokers, and current smokers were, respectively 16, 23, and 35 per 100,000 person-years [Doll et al., 1994].

How long does the excess risk of pancreatic cancer persist in former smokers? Smoking cessation does reduce the risk of pancreas cancer, but the excess risk persists for >10 years [Silverman et al., 1994].

The attributable risk, or proportion of pancreatic cancer caused by smoking, can be calculated using the formula:

$$\text{Attributable risk} = P(RR-1)/(P[RR-1]+1)$$

Where P is the proportion of the population that smoke and RR = the relative risk of pancreatic cancer in smokers versus non smokers. If P = 0.30 and RR = 2, the attributable risk is 0.3/1.3 = 23%. Smoking is the single most important life style factor leading to pancreatic cancer.

DIET AND PANCREATIC CANCER

There have been extensive investigations of the role of diet as a cause of pancreatic cancer. The incidence of pancreatic cancer varies widely throughout the world, suggesting that environmental or lifestyle factors play an important role. Some of the variation is undoubtedly due to differences in the prevalence of smoking, but it is reasonable to believe that dietary differences could also be involved. Several studies have shown that total calories and perhaps an increased amount of dietary fat could increase the risk of pancreatic cancer [Ghadirian et al., 1991; Potter, 2002]. In an experimental model, caloric restriction has reduced the frequency of preneoplastic pancreatic lesions, but similar evidence in humans is not yet available [Roebuck et al., 1993]. The nitrite content of the diet has been linked to pancreatic cancer, perhaps because increased dietary nitrites could lead to the formation of nitrosa-

mines, which are potent carcinogens [Coss et al., 2004].

Antioxidants could theoretically reduce the risk of pancreatic cancer. This hypothesis was investigated in a large cohort of middle-aged male smokers. Supplemental intake of antioxidants (alpha tocopherol and/or beta-carotene) did not reduce the risk of pancreatic cancer over a follow-up period of 5–8 years [Rautalahti et al., 1999]. A recent large prospective study of the role of folic acid in pancreatic cancer did not show any significant relationship [Skinner et al., 2004]. It is entirely possible that antioxidants and/or other vitamins or micronutrients would be effective against this or other types of cancer if administered continuously, beginning early in life.

The whole effort to obtain solid data concerning diet and cancer has been challenging, in part because of the difficulty in obtaining accurate dietary exposure information. Most dietary studies are based upon recent estimates of dietary intake, whereas it is well known that development of cancer after exposure to even a potent risk factor takes several decades. It is difficult to obtain accurate dietary information from adults about their early dietary preferences. And it is possible that maternal dietary exposure, which is generally unknown, could influence subsequent cancer development in the offspring.

OCCUPATIONAL RISK FACTORS

Only a few studies have looked at occupational exposure as a causative factor for pancreas cancer. Possible harmful exposures include chlorinated hydrocarbons, organochlorines, formaldehyde, and pesticides [Ojajarvi et al., 2000]. Some of these agents have been suspected to be risk factors for other more common tumors. In any event occupational exposure has never been considered a major factor leading to pancreatic cancer. It is probable that the total risk of pancreatic cancer arising from all types of occupational exposure is less than 5%—considerably less than the risk associated with smoking.

BACKGROUND DISEASES

Several benign medical conditions have been suggested as possibly increasing the risk of subsequently developing pancreatic cancer. These diseases include peptic ulcer disease, cholelithiasis and cholecystitis, chronic pancreatitis, and diabetes. For the latter two diseases there is sufficient evidence to support a causal relationship.

Chronic Pancreatitis and Pancreatic Cancer

Chronic pancreatitis develops in persons who have had repeated attacks of acute pancreatitis. Most patients are males who smoke and drink heavily, although "idiopathic" pancreatitis can develop in persons without any history of heavy drinking, but who carry a single mutation in a cystic fibrosis gene. Chronic pancreatitis can also develop in young persons who inherit a germ line defect on chromosome 7q35. The inheritance pattern is autosomal dominant with a penetrance of 80%. Finally, there is a type of chronic pancreatitis occurring in persons living in the southern parts of India or Africa. This disease of unknown etiology has been termed tropical pancreatitis.

In all types of pancreatitis, the risk of pancreatic cancer is elevated. For example, patients with idiopathic or alcoholic pancreatitis have a 15-fold increased risk of pancreatic cancer [Lowenfels et al., 1993]. For those patients with hereditary pancreatitis, the lifetime risk of pancreatic cancer is approximately 30%–40% [Lowenfels et al., 1997]; for patients with tropical pancreatitis the risk of pancreatic cancer is also high [Chari et al., 1994].

The link between chronic pancreatitis and pancreatic cancer is similar to the well known increased cancer in other digestive organs where there is a background inflammatory disease. For example, patients with gastritis have a significant increased risk of gastric cancer, and in similar fashion, patients with ulcerative colitis have an increased risk of colon cancer. In all instances increased cell turnover could increase the possibility of coding errors leading to deleterious mutations. Injured tissues attract inflammatory cells, which, in turn, can result in the formation of damaging free radical intermediate products. Using gene array analysis Farrow et al. [2004] have reported similar inflammatory components in both chronic pancreatitis and pancreatic cancer.

Diabetes and Pancreatic Cancer

There are two main types of diabetes, called Type I and Type II. Type I diabetes is occurs in younger individuals and is caused by destruc-

tion of pancreatic islet cells leading to insulin insufficiency, and usually requires long-term insulin therapy. This type of diabetes has not been linked to pancreatic cancer.

In contrast Type II diabetes is most frequently observed in adults, and is related to obesity and sedentary lifestyle. This type of diabetes has been linked to pancreatic cancer. Most studies have detected about a twofold increased risk of pancreatic cancer in patients with type II diabetes [Everhart and Wright, 1995; Coughlin et al., 2004].

The diabetes–pancreatic cancer relationship has been confusing because some patients with pancreatic cancer develop diabetes as a manifestation of their underlying pancreatic tumor. When this happens, the onset of diabetes is abrupt, with pancreatic cancer being discovered within a few months after the appearance of pancreatic cancer. Clinicians are well aware that the relationship between diabetes and pancreatic cancer can be bidirectional.

GENETIC FACTORS

Inherited genetic factors account for an estimated 5%–10% of all cases of pancreatic cancer. Surprisingly, BRCA2, one of the two genes implicated in familial breast cancer, is the commonest inherited gene that has been linked to pancreatic cancer [Lal et al., 2000; Hahn et al., 2003]. BRCA2 acts as a tumor suppressor gene, contributing to DNA repair and transcriptional regulation in response to DNA damage. In addition to its role in familial pancreatic cancer, this gene has also been linked to sporadic pancreatic cancer.

Do polymorphic genes play a role in inherited or sporadic pancreatic cancer? Since smoking is known to cause pancreatic cancer, it seems reasonable to suspect that polymorphic genes that detoxify carcinogens in tobacco smoke could be important preventive factors. This hypothesis is especially attractive, since probably less than 2% of smokers will ever develop pancreatic cancer. Investigators have looked at various polymorphisms in the cytochrome P-450 system, *N*-acetyltransferases, glutathione S-transferases, and uridine 5′-diphosphate glucuronosyltransferases, but the results have been inconsistent.

EARLY ONSET PANCREAS CANCER

As can be observed in Figure 3, the incidence of pancreatic cancer increases rapidly with age, with the average age of onset around 65 years. But about 10% of patients develop pancreatic cancer at or before age 50. Discovering the cause(s) of early onset pancreas cancer is an

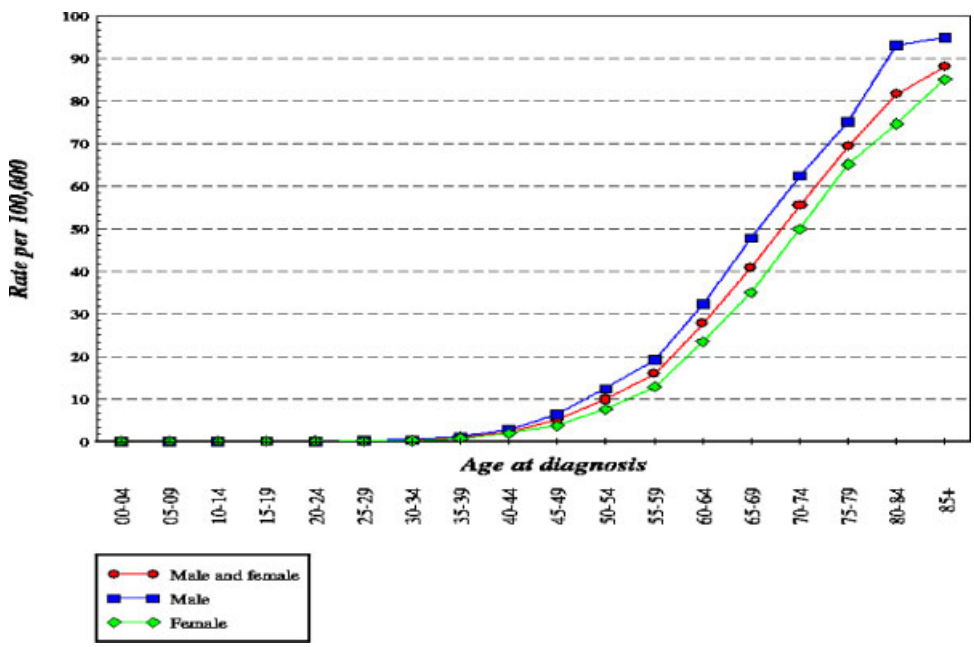

Fig. 3. Age-specific incidence rates for pancreatic cancer in the United States [Pancreatic cancer: Age-specific incidence in USA, 2003]. About 10% of pancreatic cancers occur prior to age 50. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

important research goal. At present we have limited information about the etiology of early onset pancreas cancer, but patients who are exposed to multiple risk factors are candidates for early onset pancreas cancer. For example, the hereditary form of pancreatitis carries a high risk of pancreatic cancer; if these patients smoke, then the pancreatic cancer develops about two decades sooner than in non-smokers [Lowenfels et al., 2001]. Similar findings have been noted in patients with familial pancreas cancer who smoke [Schenk et al., 2001; Rulyak et al., 2003]. These isolated findings suggest an interaction between two or more risk factors. We need additional investigation focusing on underlying mechanisms such as genetic polymorphisms that could affect degradation of tobacco products into carcinogenic substances [Duell et al., 2002]. Genetic factors are likely to play an important role in early onset of pancreas cancer, where known risk factors such as smoking, are absent.

UNANSWERED RESEARCH QUESTIONS

Reviewing known risk factors for pancreatic cancer discloses how little we know about the causes for this lethal cancer. Areas that need additional research include the following.

Detecting Agents That Reduce the Risk of Pancreatic Cancer

In other digestive tract organs such as the colon, aspirin or Cox2 inhibitors have been shown to reduce the risk of cancer. With respect to pancreatic cancer, the results are not as clear; in most studies prolonged aspirin intake appears to reduce the risk of pancreatic cancer, but at least one study has failed to confirm this finding [Anderson et al., 2002; Jacobs et al., 2004; Schernhammer et al., 2004].

H. pylori

H. pylori has been classified as a known bacterial carcinogen because it is strongly linked to gastric cancer. Could this ubiquitous agent also cause pancreatic cancer? Some studies have found a positive association between infection with *H. pylori* and pancreatic cancer, but additional research will be needed to determine if this is a true causal relation [Raderer et al., 1998; Stolzenberg-Solomon et al., 2001].

Early Diagnosis of Pancreatic Cancer—Proteomics

One of the major problems with pancreatic cancer concerns the inability to arrive at an early diagnosis. Routine endoscopic screening procedures that proved to be effective for other digestive tract cancers are not available for the pancreas. Unlike the liver, where needle biopsy can be easily and safely performed, biopsy of the pancreas is much more difficult and can lead to leakage of pancreatic enzymes. We need to develop new modalities that can lead to an early diagnosis of pancreatic cancer. New radiologic approaches such as spiral computerized tomography are being used to detect ever smaller lesions. But a more refined approach would be to detect markers associated with early onset pancreatic cancer in either the serum or in pancreatic juice. Molecular markers, as detected by proteomics have the potential to detect pre-malignant pancreatic disease, affording an opportunity for cure rather than palliation. This promising area needs additional research effort [Rosty and Goggins, 2004].

Extreme Aggressivity

Tumors in the pancreas and in the biliary tract share a similar embryologic background and they also share an additional property: both tumor types have extremely high mortality rates. Even small tumors have a poor prognosis, suggesting that these most of these cancers are already disseminated at the time of diagnosis. At present we cannot explain why these tumors are so highly aggressive.

SUMMARY

Pancreas cancer remains one of our major oncologic challenges because risk factors have been firmly identified for only a fraction of all causes. Furthermore, because of its location in a remote part of the abdomen, screening is not as easy as for other digestive tract organs. Smoking is a well-established risk factor, doubles the risk of pancreatic cancer, and current established germ line mutations cause about 5%–10% of all cases. Having a first degree relative with pancreatic cancer definitely increases the risk, and there is currently an intensive search to detect the underlying gene or genes that cause familial pancreatic cancer. Pre-existing benign diseases that have been linked to pancreatic cancer include chronic

pancreatitis and diabetes, but these two diseases account for only a small fraction of the total burden of pancreatic cancer. Widespread international differences in pancreatic cancer rates are likely to be due to lifestyle factors such as smoking and diet.

REFERENCES

Anderson KE, Johnson TW, Lazovich D, Folsom AR. 2002. Association between nonsteroidal anti-inflammatory drug use and the incidence of pancreatic cancer. J Natl Cancer Inst 94(15):1168–1171.

Boyle P, Maisonneuve P, Bueno dM, Ghadirian P, Howe GR, Zatonski W, et al. 1996. Cigarette smoking and pancreas cancer: A case control study of the search programme of the IARC. Int J Cancer 67(1):63–71.

Chari ST, Mohan V, Pitchumoni CS, Viswanathan M, Madanagopalan N, Lowenfels AB. 1994. Risk of pancreatic carcinoma in tropical calcifying pancreatitis: An epidemiologic study. Pancreas 9:62–66.

Coss A, Cantor KP, Reif JS, Lynch CF, Ward MH. 2004. Pancreatic cancer and drinking water and dietary sources of nitrate and nitrite. Am J Epidemiol 159(7): 693–701.

Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. 2004. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol 159(12): 1160–1167.

Doll R, Peto R, Hall E, Wheatley K, Gray R. 1994. Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. BMJ 309(6959):911–918.

Dong M, Nio Y, Tamura K, Song MM, Guo KJ, Guo RX, et al. 2000. Ki-ras point mutation and p53 expression in human pancreatic cancer: a comparative study among Chinese, Japanese, and Western patients. Cancer Epidemiol Biomarkers Prev 9(3):279–284.

Duell EJ, Holly EA, Bracci PM, Liu M, et al. 2002. A population-based case-control study of polymorphisms in carcinogen-metabolizing genes, smoking and pancreatic adenocarcinoma risk. J Natl Cancer Inst 94:297–306.

Engeland A, Andersen A, Haldorsen T, Tretli S. 1996. Smoking habits and risk of cancers other than lung cancer: 28 years' follow-up of 26,000 Norwegian men and women. Cancer Causes Control 7(5):497–506.

Everhart J, Wright D. 1995. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA 273(20):1605–1609.

Farrow B, Sugiyama Y, Chen A, Uffort E, Nealon W, Mark EB. 2004. Inflammatory mechanisms contributing to pancreatic cancer development. Ann Surg 239(6):763–769.

Ghadirian P, Thouez JP, PetitClerc C. 1991. International comparisons of nutrition and mortality from pancreatic cancer. Cancer Detect Prev 15:357–362.

Hahn SA, Greenhalf B, Ellis I, Sina-Frey M, Rieder H, Korte B, et al. 2003. BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst 95(3):214–221.

Hingorani SR, Petricoin EF, Maitra A, Rajapakse V, King C, Jacobetz MA, et al. 2003. Preinvasive and invasive ductal pancreatic cancer and its early detection in the mouse. Cancer Cell 4(6):437–450.

Hruban RH, van Mansfeld AD, Offerhaus GJ, van Weering DH, Allison DC, Goodman SN, et al. 1993. K-ras oncogene activation in adenocarcinoma of the human pancreas. A study of 82 carcinomas using a combination of mutant-enriched polymerase chain reaction analysis and allele-specific oligonucleotide hybridization. Am J Pathol 143(2):545–554.

Hruban RH, Adsay NV, Albores-Saavedra J, Compton C, Garrett ES, Goodman SN, et al. 2001. Pancreatic intraepithelial neoplasia: A new nomenclature and classification system for pancreatic duct lesions. Am J Surg Pathol 25(5):579–586.

Jacobs EJ, Connell CJ, Rodriguez C, Patel AV, Calle EE, Thun MJ. 2004. Aspirin use and pancreatic cancer mortality in a large United States cohort. J Natl Cancer Inst 96(7):524–528.

Lal G, Liu G, Schmocker B, Kaurah P, Ozcelik H, Narod SA, et al. 2000. Inherited predisposition to pancreatic adenocarcinoma: Role of family history and germ-line p16, BRCA1, and BRCA2 mutations. Cancer Res 60(2): 409–416.

Longnecker DS, Karagas MR, Tosteson TD, Mott LA. 2000. Racial differences in pancreatic cancer: Comparison of survival and histologic types of pancreatic carcinoma in Asians, blacks, and whites in the United States. Pancreas 21(4):338–343.

Lowenfels AB, Maisonneuve P. 2004. Epidemiology and prevention of pancreatic cancer. Jpn J Clin Oncol 34(5):238–244.

Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, et al. 1993. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med 328:1433–1437.

Lowenfels AB, Maisonneuve P, DiMagno EP, Elitsur Y, Gates LKJ, Perrault J, et al. 1997. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst 89(6):442–446.

Lowenfels AB, Maisonneuve P, Whitcomb DC, Lerch MM, DiMagno EP. 2001. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. JAMA 286(2):169–170.

Ojajarvi IA, Partanen TJ, Ahlbom A, Boffetta P, Hakulinen T, Jourenkova N, et al. 2000. Occupational exposures and pancreatic cancer: A meta-analysis. Occup Environ Med 57(5):316–324.

Pancreatic cancer: Age-specific incidence in USA. 2003. http://seer.cancer.gov/faststats/html/inc_pancreas.html. 1–11.

Potter JD. 2002. Pancreas cancer—We know about smoking, but do we know anything else? Am J Epidemiol 155(9):793–795.

Raderer M, Wrba F, Kornek G, Maca T, Koller DY, Weinlaender G, et al. 1998. Association between *Helicobacter pylori* infection and pancreatic cancer. Oncology 55(1):16–19.

Rautalahti MT, Virtamo JR, Taylor PR, Heinonen OP, Albanes D, Haukka JK, et al. 1999. The effects of supplementation with alpha-tocopherol and beta-carotene on the incidence and mortality of carcinoma of the pancreas in a randomized, controlled trial. Cancer 86(1):37–42.

Roebuck BD, Baumgartner KJ, MacMillan DL. 1993. Caloric restriction and intervention in pancreatic carcinogenesis in the rat. Cancer Res 53(1):46–52.

Rosty C, Goggins M. 2004. Identification of differentially expressed proteins in pancreatic cancer using a global proteomic approach. Methods Mol Med 103:189–198.

Rulyak SJ, Lowenfels AB, Maisonneuve P, Brentnall TA. 2003. Risk factors for the development of pancreatic cancer in familial pancreatic cancer kindreds. Gastroenterology 124:292–299.

Schenk M, Schwartz AG, O'Neal E, Kinnard M, Greenson JK, Fryzek JP, et al. 2001. Familial risk of pancreatic cancer. J Natl Cancer Inst 93(8):640–644.

Schernhammer ES, Kang JH, Chan AT, Michaud DS, Skinner HG, Giovannucci E, et al. 2004. A prospective study of aspirin use and the risk of pancreatic cancer in women. J Natl Cancer Inst 96(1):22–28.

Silverman DT, Dunn JA, Hoover RN, Schiffman M, Lillemoe KD, Schoenberg JB, et al. 1994. Cigarette smoking and pancreas cancer: A case-control study based on direct interviews. J Natl Cancer Inst 86(20):1510–1516.

Skinner HG, Michaud DS, Giovannucci EL, Rimm EB, Stampfer MJ, Willett WC, et al. 2004. A prospective study of folate intake and the risk of pancreatic cancer in men and women. Am J Epidemiol 160(3):248–258.

Stolzenberg-Solomon RZ, Blaser MJ, Limburg PJ, Perez-Perez G, Taylor PR, Virtamo J, et al. 2001. *Helicobacter pylori* seropositivity as a risk factor for pancreatic cancer. J Natl Cancer Inst 93(12):937–941.

Time trends for pancreatic cancer in the USA. 2003. www.seer.cancer.gov. 1–11.