MINI-REVIEW

An Epidemiological Overview of Environmental and Genetic Risk Factors of Pancreatic Cancer

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Abstract

This paper overviewed risk factors of pancreatic cancer. Both genetic and environmental factors may be playing significant roles in the development of pancreatic cancer. Cigarette smoking has been established as a major risk factor for pancreatic cancer, based on findings from almost all epidemiological studies. Long-term smoking cessation may reduce the risk. The evidence that alcohol drinking and coffee consumption increase the risk is not sufficient, although an association with higher level of consumption remains a possibility. Diabetes mellitus, long-standing diabetes in particular, may be a risk factor for pancreatic cancer. Individuals with hereditary pancreatitis or non-hereditary chronic pancreatitis are possibly at increased risk of pancreatic cancer. Higher intake of meat and fat may be associated with an increased risk, while consumption of fruits/vegetables appears to have a protective effect. Individuals with mutations or deletion in such genes as K-ras, p16, p53, DPC4, and BRCA2 increased the risk of developing pancreatic cancer. Cigarette smoking may play a role in the development of these mutations.

Key Word: pancreatic cancer - review risk factor - cigarette smoking

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Pancreatic cancer has shown a marked increase in both incidence and mortality over the last 4 decades in Japan (Lin et al., 1998). It is the fifth leading cause of cancer death among males and the seventh among females, accounting for over 16,000 deaths annually (Lin et al., 1998). The etiology of pancreatic cancer remains largely unknown. To identify factors that increase the risk of pancreatic cancer is important, not only to understand the etiology of the disease, but also to improve its detection, treatment and prevention at last. In European countries and the United States, a considerable number of epidemiological studies have been conducted to identify environmental factors that contributed to pancreatic cancer development. According to these studies, cigarette smoking has been consistently reported as a risk factor for pancreatic cancer. Other possible risk factors include family history of pancreatic cancer, long-standing diabetes, and hereditary and chronic pancreatitis. A number of other factors have also been implicated, including diet and nutrition, heavy alcohol and coffee consumption, and certain occupational exposures, but these findings have been inconsistent. Genetic polymorphism and specific risk factors have yet to be identified.

This paper provides a review on environmental and genetic factors that have been reported to be associated with risk of pancreatic cancer. Besides, we will also summarize the results of epidemiological studies on pancreatic cancer in Japan.

Age and Gender

Risk of pancreatic cancer increased with an advancing age. Approximately 80% of the patients occur between ages

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60 and 80, and those aged below 40 years old are extremely rare (Gold, 1995). Pancreatic cancer occurs more frequently in males than in females. Mortality rate among males is approximately 1.7-times higher than among females in Japan (Lin et al., 1998).

Family History

Pancreatic cancer has been shown to aggregate in families (Ghadirian et al., 1991). Several case-control studies (Schenk et al., 2001; Fernandez et al., 1994; Silverman et al., 1999) have been conducted to examine whether a positive family history of pancreatic cancer was a risk factor for pancreatic cancer in first-degree relatives. Schenk et al.(Schenk et al., 2001) reported that a positive family history of pancreatic cancer approximately doubled the risk (OR, 2.5 ; 95% CI, 1.3-4.7), and the OR increased to 8.2 (95% CI, 2.1-31.1) for relatives who ever smoked and were related to a case proband who was diagnosed before age 60 years. In another case-control studies (Silverman et al., 1999), case patients with a family history has a statistically increased risk of pancreatic cancer (OR, 3.2 ; 95% CI 1.8-5.6).

Tobacco, Alcohol and Coffee Consumption

Cigarette Smoking

Cigarette smoking has been consistently reported, in almost all epidemiological studies, to be associated with an increased risk of pancreatic cancer. The proportion of pancreatic cancer attributable to cigarette smoking ranged from 25-39% (Fernandez et al., 1996). Since 1985, at least 27 investigations, including 19 case-control studies (see Table 1) and 8 cohort studies (see Table 2), have examined the relationship between cigarette smoking and pancreatic cancer. The odds ratios for current smokers ranged from 1.4 to 5.7 in case-control studies. The dose-response relationship was, however, generally weak among these studies. The cohort studies have corroborated this positive association. In these cohort studies, in general, current smokers were at increased risk compared with non-smokers, though the strength of association was somewhat weak. The relative risk ranged from 1.3 to 3.9 for current smokers, and a significant dose-response relationship was observed only in 2 of 8 studies (Fuch et al., 1996; Harnack et al., 1997).

Based on these findings, cigarette smoking is probably a weak pancreatic cancer carcinogen. It has been suggested that cigarette smoking plays its role in the later stages of carcinogenic process (Mack et al., 1986). Howe et al.(Howe et al., 1991) found that limiting cigarette smoking within the 15 years prior to diagnosis considerably strengthened the association and led to a much clearer does-response relationship. A significant, positive trend in risk with the increasing pack-years of smoking was also observed in another prospective cohort study (Fuch et al., 1996), when the analysis was confined to cigarette smoking within the past 15 years. Silverman et al.(Sliverman et al., 1994) found that duration smoked within 10 years of diagnosis/interview only had a small, independent effect on risk, but rather total duration, including more than 10 years prior to diagnosis/ interview was an important determinant of risk.

Smoking cessation appears to reduce the risk of pancreatic cancer (Silverman et al., 1994; Fuch et al., 1996; Harnack et al., 1997; Nilson and Vatten, 2000). Fuchs et al. and Nilsen et al. reported a much more rapid reduction in risk following smoking cessation. They showed that the relative risk among former smokers approached that for never smokers after less than 10 years. While in another case-control study (Silverman et al., 1994), smokers who had quit for more than 20 years still experienced a 30% higher risk of pancreatic cancer than nonsmokers. One possible reason for the different pattern of decline in risk is that the speed may be overestimated in cohort studies because years since smoking cessation for ex-smokers were always fixed at the baseline survey (Wakai et al., 2001). Though the length of time for the risk among ex-smokers to approach the risk level of non-smokers may differ across studies, the reduction in risk after long-term smoking cessation supports a causal relationship.

There have been few epidemiological studies in Japan searching into the environmental etiology of pancreatic cancer. The first large-scale cohort study on lifestyle factors and cancer was conducted by Hirayama et al.(Hirayama, 1989) between 1965 and 1980. During the follow-up period, 679 deaths from pancreatic cancer were identified. Daily cigarette smoking was significantly associated with an increased risk of pancreatic cancer (RR,1.5, 90% CI,1.3-1.8). Risks that could be attributable to cigarette smoking were estimated to be 28.3% in males and 6.1% in females. In another multi-institute case-control study, Mizuno et al.(Mizuno et al., 1992) reported that the odds ratio for current smokers was 2.4 (95% CI, 1.1-5.3), relative to non-smokers, after adjustment for sex, age and place of enrollment. Despite few studies available to date, cigarette smoking is believed to be an important risk factor for pancreatic cancer in Japan, too. The mechanisms by which cigarette smoking influences pancreatic carcinogenesis are not clear. Studies have shown induction of pancreatic tumors by tobacco-specific nitrosamines both in human (Hecht and Hoffman, 1991) and in animals (Riverson et al., 1988), and autopsy studies have shown substantial pancreatic tissue damages among smokers compared with non-smokers (Auerback and Garfinkel, 1986). It has been postulated that tobacco-specific carcinogen reach the pancreas either through the blood or through refluxed bile that is in close contact with the pancreatic duct (Schulze et al., 1992).

Considering the epidemiological evidence to date, cigarette smoking is an established risk factor for pancreatic cancer. Long- term smoking cessation may reduce the risk.

Alcohol consumption

The role of alcohol drinking in pancreatic cancer etiology had been a focus of numerous epidemiological studies. Most of the recent studies have found little or no support for a

Table 1. Cigarette Smoking and the Risk of Pancreatic Cancer: Case-Control Studies

Author, year and place	No of cases	No of controls	Comparision	OR (95% CI)
Mack TM et al, 1986 Los Angeles, US	490 subjects	490 healthy controls	Never smokers/ current smokers >1 pack daily	5.7 (2.2-15.0)
Falk RT et al, 1988 Louisiana, US	203 males and 160 females	1,234 hospital controls	Never smokers/current smokers ≥26 cigarettes	2.0
Clavel F et al, 1989 France	98 males and 63 females	161 hospital controls	Never smokers/current smokers 1-20 cig./day among men	1.7 (0.8-3.7)
Olsen G et al, 1989 Minneapolis-St. Paul, US	212 subjects	220 population controls	Never smokers/current smokers ≥2 packs per day	3.9 (1.2-13.0)
Farrow D et al, 1990, US	148 males	188 population controls	Never smokers/current smokers	3.2 (1.8-5.7)
Mesquita H et al, 1991 Netherlands	94 males and 82 females	487 population controls	Never smokers/lifetime smokers more than 111,200 cigarettes	1.7 (0.95-3.1)
Ghadirian P et al, 1991 Quebec, Canada	97 males and 82 females	239 population controls	Never smokers/current smokers in the highest quintile of number of cigarettes	5.2 (1.7-16.1)
Howe G et al, 1991 Toronto, Canada	141 males and 108 females	505 population controls	Never smokers/ current smokers	2.5 (1.5-3.9)
Mizuno S et al, 1992 Japan	68 males and 56 females	124 hospital controls	Never smokers/light smokers <13 cigarettes among men	4.5 (1.5-13.2)
Kalapothaki V et al, 1993 Greece	115 males and 66 females	66 hospital controls and 66 visitor controls	Never smokers/current smokers21+ cigarettes	1.4 (0.8-2.4)
Zatonski W et al, 1993 Opole, Poland	68 males and 42 females	195 population controls	Never smokers/ever smokers	1.9 (1.2-3.1)
Silverman D et al, 1994, US	526 subjects	2,153 population controls	Never smokers/current smokers	1.8 (1.4-2.4)
Ji B et al, 1995 Shanghai, China	264 males and 187 females	1,552 population controls	Nonsmoker/current smoker among men Nonsmoker/current smoker among women	1.6 (1.1-2.2) 1.4 (0.9-2.4)
Lee C et al, 1996 Taipei, Taiwan	222 males and 60 females	282 hospital controls	Non-smokers/current smokers	2.3 (1.6-3.3)
Boyle P et al, 1996 IARC search programme	823 subjects	1,679 population controls	Never smokers/ever smokers	2.7 (1.95-3.7)
Muscat JE et al, 1997 US	484 males and females	954 hospital controls	Never smokers/current smokers among men Never smokers/current smokers among women	1.6 (1.1-2.4) 2.3 (1.4-3.5)
Partanen T et al, 1997, Finland	662 subjects	1,770 hospital controls	Never smokers/current smokers	1.96 (1.6-2.4)
Talamini G et al, 1999, Italy	69 males	700 population controls	Never smokers/smokers >10 cigarettes	4.8 (2.7-8.3)
Villeneuve PG et al, 2000 Canada	322 males and 261 females	4,813 population controls	Never smokers/cigarettes pack-years>35 among males Never smokers/cigarettes pack-years>23 among females	1.5 (1.0-2.1) 1.8 (1.3-2.7)

causal relationship between regular drinking and risk of pancreatic cancer. In 1988, an IARC Working Group evaluated the studies to that date and concluded that consumption of alcoholic beverages was unlikely to be causally related to pancreatic cancer (IARC monograph, 1991). Nevertheless, at least 7 studies have suggested that heavy alcohol drinking may be related to an increased risk (Olsen et al., 1989; Zheng et al., 1993; Heuch et al., 1983; Cuzick et al., 1989; Adami et al., 1992; Tonnsen et al., 1994; Silverman et al., 1995). Among these studies, two prospective studies showed a statistically significant increase in risk with higher total alcohol intake (Zheng et al., 1993; Harnack et al., 1997). Another population-based case-control study conducted in the United States (Silverman et al., 1995) found that alcohol drinking at the levels typically consumed by the general population is probably not a risk factor for

Table 2. Cigarette Smoking and the Risk of Pancreatic Cancer: Cohort Studies

Author, year and place	Size of cohort No. of cases or deaths	Comparision	RR (95% CI)
Hirayama T, 1989 Japan	122,261 men and 142,857 women 679 deaths	Never/Current smokers	1.5 (1.3-1.8)
Zheng et al, 1993 USA	17,633 white men 56 deaths	Never smoker/<25 cigarettes/day Never smoker/25+ cigarettes/day	1.4 (0.6-3.2) 3.9 (1.5-10.3)
Shibata et al, 1994 California, USA	13,979 residents of a retirement community: 65 incident cases	Never smoked/ recent quitters and current smokers	1.2 (0.7-2.2)
Fuchs et al, 1996 USA	118,339 women and 49,428 men 186 cases	Never smokers/ current smokers	2.5 (1.7-3.6)
Engeland et al, 1996 Norway	26,000 men and women 224 cases	Never smoker/current smoker	1.1 (0.8-2.2)
Harnack et al, 1997 Iowa, USA	33,976 postmenopausal women 66 cases	Never/present	2.4 (1.3-4.2)
Shgapiro J et al, 2000 USA	137,243 men 385 deaths	Never smoker/current smoker	1.3 (0.9-1.9)
Nilson T et al, 2000 Norway	31,000 men and 32,374 women 166 cases	Never/Current smokers	2.1 (1.2-3.6)

pancreatic cancer, but heavy alcohol drinking may be related to pancreatic cancer risk. In this study, blacks and whites who drank at least 57 drinks/week had ORs of 2.2 (95% CI 0.9-5.6) and 1.4 (95% CI 0.6-3.2), respectively, as compared with non-drinkers. Further studies are needed to determine whether heavy alcohol drinking is causally related to pancreatic cancer.

No specific biological mechanism has been proposed for an effect of alcohol drinking on pancreatic cancer risk. As alcohol consumption is an established risk factor for chronic pancreatitis, and chronic pancreatitis has been shown to be associated with increased risk of pancreatic cancer in some studies (Talamini et al., 1999; Bansal et al., 1995), it is plausible that biological pathway might involve pancreatitis as an intermediate step.

In Japan, no overall effect was found in Hirayama's cohort study, but the small group of whiskey drinkers was found to be at increased risk for pancreatic cancer. Alcohol drinking was not related to pancreatic cancer risk in a multi-institute case-control study conducted in Japan (Mizuno et al., 1992).

Overall, the evidence that alcohol drinking increases the risk of pancreatic cancer is not sufficient, although higher level of consumption remains its possibility.

Coffee consumption

Since MacMahon reported a 2-3 fold increase in pancreatic cancer risk by three or more cups of coffee per day in 1981 (MacMahon et al., 1981), the association of coffee consumption with pancreatic cancer has drawn considerable attention in the subsequent decade. Reports on this issue have produced controversial evidence. The positive association has been reported in several studies, with the 2-3 fold risk for those who drink 5 cups per day (Falk et al., 1998; Lee et al., 1996; Ghgadirian et al., 1991; Zheng et al., 1993; Shibata et al., 1994; MacMahon et al., 1981; Gold et al., 1985; Lyon et al., 1992; Hsieh et al., 1986; Gullo et al., 1995). A dose-response relationship was observed in some of these studies. The possibility, however, remains that the observed increased risk with higher coffee consumption may be the result of residual confounding by smoking and dietary factors. For example, fruit consumption, which probably reduced the pancreatic cancer risk, has been shown to be lower in heavy coffee drinker, and heavy coffee drinkers are more likely to be smokers (Falk et al., 1998). In large number of recent epidemiological studies (Farrow and Davis, 1990; Olsen et al., 1989; Zatonski et al., 1993; Villeneuve et al., 2000; Kalapothaki et al., Zheng et al., 1994; Shibata et al., 1994; Mill et al., 1988; Hiatt et al., 1988; Friedman and van den Eeden SK, 1993; Veccia et al., 1987), including at least 5 cohort studies, no positive association has been identified between coffee consumption and pancreatic cancer risk.

Interestingly, a recent case-case study by Porta et al. (Porta et al., 1999) found that heavy coffee drinkers with pancreatic cancer showed a greater proportion of mutations of the ras cancer gene than patients who did not drink coffee. Given the highest frequency of K-ras gene mutations identified in pancreatic cancer (Caldas and Kern, 1995), the authors suggested that an association may exist in pancreatic cancer between K-ras mutation and regular coffee intake. As this is the first occasion that such a finding is reported, longitudinal designs with repeated measures will be needed to confirm this association.

In Japan, two case-control studies (Mizuo et al., 1992; Nishi et al., 1996) and one cohort study (Hirayama, 1989) have examined the relation between coffee drinking and pancreatic cancer. No consistent association was observed in 2 of 3 studies. Nishi et al. reported that dose-response relationship was U-shaped between coffee drinking and pancreatic cancer risk. Among the four categories (never, occasionally, 1-2 cups/day and 3+cups/day), the lowest relative risk was found among occasional drinkers, with ORs of 0.2 (95% CI, 0.1-0.4) for males and 0.5 (95% CI, 0.2-1.4) for females. Furthermore, when the analysis was limited to smokers, an increased risk was observed only for those who consumed 3+ cups/day (OR, 2.0; 95% CI, 0.9-4.2). It appeared accordingly that small amounts of coffee consumption would not be related to the risk of pancreatic cancer.

Overall, epidemiological evidence did not indicate any significantly increased risk of pancreatic cancer with coffee intake, although a weak association with higher levels of consumption remains its possibility.

Medical conditions

Diabetes mellitus and chronic pancreatitis are widely investigated for their possible role in the development of pancreatic cancer. In addition, allergic conditions (Dai et al., 1995), cholecysititis (Kalapothaki et al., 1993; Schattner et al., 1997), cholecystectomy (Shibata et al., 1994) and tonsillectomy (Farrow and Davis, 1990) have been sporadically reported to be associated with pancreatic cancer.

Diabetes mellitus

Pancreatic cancer is the most common subject of studies on diabetes as a risk factor because both pancreatic cancer and diabetes involve the same organ. The association between diabetes and pancreatic cancer has been evaluated in more than 30 studies, with most indicating a positive relationship (Silverman et al., 1999; Fernandez et al., 1996; Farrow and Davis, 1990; Lee et al., 1996; Mack et al., 1986; Kalapothaki et al., 1993; Shibata et al., 1994; Chow et al., 1995; Chow et al., 1999; Calee et al., 1998; Cuzick et al., 1989; Everhart and Wright, 1995). The RRs ranged from 0.8-6.1 for the diabetics compared with the non-diabetics. In 1995, a meta-analysis by Everhart and Wright showed that the diabetics diagnosed at least 5 years prior to the diagnosis of cancer had a pooled relative risk of 2.2 (95% CI 1.2-3.2). A 1998 study from American Cancer Society found a small but persistently increased risk of death from pancreatic cancer among the diabetics, and concluded that diabetes may be a true, but modest, risk factor for pancreatic cancer (Calee et al., 1998). Silverman et al. (Silverman et al., 1999) found a significant 50% increased risk of pancreatic cancer among those diagnosed with diabetes at least 10 years prior to the diagnosis of cancer.

A methodological weakness common to the most studies of diabetes and pancreatic cancer is the poor characterization of diabetes, which may result in exposure misclassification. To overcome this weakness, Gapstur et al.(Gapstur et al., 2000), using 50g oral glucose load as diagnostic criteria in their prospective cohort study, observed a significant dose-response relationship between postload plasma level of glucose and subsequent risk of pancreatic cancer mortality. It is likely, however, that diabetes could just be a consequence of pancreatic cancer. Pancreatic cancer can cause diabetes by destroying islet cells or by causing peripheral resistance to insulin, which may explain why diabetes can appear before the symptoms of the pancreatic tumor.

The mechanism by which long-standing diabetes causes pancreatic cancer is uncertain. One possibility is that exposure to insulin promotes growth in human pancreatic cell lines (Fisher et al., 1996). Hyperinsulinaemia is characterized by both obesity and non-insulin-dependent diabetes mellitus (NIDDM), and may play a role in pancreatic cancer carcinogenesis.

Concluding from the available evidence, diabetes mellitus may be a risk factor for pancreatic cancer as well as a consequence of pancreatic cancer. Long-standing diabetes increases the risk of pancreatic cancer.

In Japan, there have been no analytic epidemiological studies ever conducted to explore the association between diabetes and pancreatic cancer. If diabetes is a true risk factor for pancreatic cancer, the increase in pancreatic cancer incidence during the recent decades can be partly explained by the increasing number of diabetics. Further prospective studies are needed to clarify their association.

Chronic Pancreatitis

The existence of a clear association between chronic pancreatitis and subsequent risk of pancreatic cancer has been documented in a number of epidemiological studies (Talamini et al., 1999; Bansal and Sonnenberg, 1995; Lowenfenls et al., 1993; Ekbom et al., 1994). Bansal and Sonnenberg compared the occurrence of pancreatic cancer in 2,639 patients with chronic pancreatitis and a matched control group of 7,774 subjects, and found that patients with chronic pancreatitis was significantly associated with increased risk of pancreatic cancer: with the OR of 2.2 (95% CI, 1.4-3.5). In a multicenter cohort study of 2,015 subjects with chronic pancreatitits, a total of 56 pancreatic cancers were identified during a mean follow-up time of 7.4.2 years, which yielded a standardized incidence ratio of 26.3 (95%CI 19.9-34.2) (Ekbom et al., 1994). Risk of pancreatic cancer is substantially increased in subjects with chronic pancreatitis. When compared with general population in another prospective cohort study (Talamini et al., 1999), patients with chronic pancreatitis have also shown an excessive incidence of pancreatic cancer.

In chronic pancreatitis, there appears to be cellular dysfunction, glandular destruction, and presumably, increased cell turnover (Andren-Sandberg et al., 1997). Increased cell division has been suggested as a potential precursor of cancer (Andren-Sandberg et al., 1997).

Therefore, it is likely that the inflammatory process inherent to chronic pancreatitis may be a contributing factor to pancreatic cancer development.

Dietary and nutritional factors

Dietary factors

To date, numerous studies have been conducted to explore the relationship between dietary intake and pancreatic cancer (Howe et al., 1992; Ghadirian et al., 1995; Silverman et al., 1998; Ohba et al., 1996; Howe and Burch, 1996; Ghadirian et al., 1991; Howe et al., 1990; Bueno de Mesquita HB et al., 1990, 1991; Farrow et al., 1990; Zatonski et al., 1991; Kalapothaki et al., 1991; Ji et al., 1995; Baghurst et al., 1991; Lyon et al., 1993). Due to the high fatality rate and the difficulty of dietary research, the role of diet and nutrition remains equivocal. A large collaborative case-control study (Howe et al., 1992) reported a strong dose-response increase in risk with increasing total energy intake (cigarette smoking-adjusted ORs of 1.2, 1.2, 2.0 and 2.1 for increasing quintiles of intake). A statistically significant positive trend in risk was observed with increasing caloric intake in a recent case-control study (Silverman et al., 1998), with subjects in the highest quartile of caloric intake experiencing a 70% higher risk than those in the lowest quartile. At least 7 case-control studies have examined dietary cholesterol (Ghadirian et al., 1991; Howe et al., 1990; Bueno de Mesquita HB et al., 1990, 1991; Farrow et al., 1990; Zatonski et al., 1991; Kalapothaki et al., 1991;). Four of seven showed an increased risk by higher cholesterol intake. Based on the IRAC Search Program, higher intake of cholesterol was significantly associated with an increased risk of pancreatic cancer (Howe et al., 1992). The odds ratio (adjusted for energy and cigarette smoking) for the highest quartile versus the lowest quartile was 1.5 (95% CI, 1.1-2.0). As for carbohydrate and protein, no consistent positive results were available. Vitamin C and fiber were relatively consistent in their protective role across studies. In Shibata's cohort study (Shibata et al., 1994), the highest vitamin C intake (>220 mg/d) showed a RR of 0.8 (95% CI, 0.4-1.4), after adjustment for cigarette smoking and energy intake. According to Howe's review (Howe and Burch, 1996), the most consistently reported nutrients across studies were vitamin C and fiber.

In addition to nutrients, a number of studies have focused on the role of specific foods or food groups (Zheng et al., 1993; Hirayama, 1989; Mill et al., 1988; Bueno de Mesquita HB et al., 1990, 1991; Baghurst et al., 1991; Lyon et al., 1993). Given the variety of food and food groups, it is difficult to examine in a consistent fashion. Nevertheless, three prospective studies have found an increased risk with greater consumption of meat (Zheng et al., 1993; Hirayama ,1989; Mill et al., 1988). In Hirayama's cohort study, daily consumption of meat was associated with an increased risk, compared with no consumption. In another case-control study conducted in Japan (Ohba et al., 1996), intake of meat and animal viscera also increased the risk, while vegetables and the traditional Japanese foods were seemingly protective.

Considering the epidemiological evidence, the role of diet in pancreatic cancer remains controversial. A diet high in meat and fat may increase pancreatic cancer risk, while fruits/vegetables and dietary fiber appear to have a protective effect.

Serum micronutrients

Maintaining adequate folate status may reduce the risk of pancreatic cancer. Stolzenberg et al.(Stolzenberg-Solomen et al., 1999) found statistically significant reduced risk for pancreatic cancer associated with more adequate folate status in a prospective cohort of male smokers. A dose-response relationship was evident, with the OR of 0.5 (95% CI, 0.2-0.8) for the highest tertile versus the lowest tertile. Mechanisms by which folate deficiency may influence pancreatic carcinogenesis remains speculative. Folate and vitamin B12 are nutritional components involved in methylation and synthesis of DNA. Imbalances in DNA methylation may affect chromosome stability and gene expression throughout carcinogenesis (Baylin et al., 1998). DNA hypo- and hyper- methylation may increase the suscepbility of genes to mutations (Baylin et al., 1998). The protective association between fruits and vegetables, the major folate sources, and pancreatic cancer suggests that factors influencing methylation might be related to the development of pancreatic cancer (Howe and Burch, 1996).

Using a nested case-control design, Burney et al. (Burney et al., 1989) examined the association of retinol, total carotenoids, b-carotene, licopene, vitamin E and selieum with subsequent development of pancreatic cancer. They found that lower serum licopene and selieum were associated with an increased pancreatic cancer risk. The protective effect of licopene was the greatest among non-smokers, and remained as such when smoking was taken into account. Selieum has been shown to be protective against pancreatic cancer carcinogenesis in several animal models (Woutersen et al., 1999). Nevertheless, there has been no corroborating evidence from other human studies suggesting a role for lycopene and selieum in pancreatic cancer carcinogenesis. The protective effect of folate and selieum needs to be confirmed in further prospective studies.

Occupational exposure

Occupational exposures may contribute to the risk of pancreatic cancer, although no consistent pattern has been identified. According to Ojajavri's meta-analysis (Ojajarvi et al.,2000), the etiological fraction due to occupational exposures was estimated as 12%. A nested case-control study of chemical manufacturing workers (Garabrant et al., 1992) indicated that DDT is an independent risk factor for pancreatic cancer. The reflux of biliary secretion containing DDT metabolites into the proximal pancreatic duct was proposed as a potential route of exposure (Ojajarvi et al.,

2000). Recently, another two case-control studies have consistently showed that exposure to chlorinated organics was associated with an increased risk of pancreatic cancer (Porta et al., 1999; Hoppin et al., 2000). Organochlorine compounds such as DDT, DDE, and some PCBs could play a part in the pathogenesis through K-ras activation (Hoppin et al., 2000). Besides, several studies have reported that heavy exposure to certain pesticides, certain dyes, and certain chemicals related to gasoline may also increase the risk of pancreatic cancer (Fryzek et al., 1997; Kauppinen et al., 1995).

Genetic factors

About 3% to 5% of pancreatic cancers are thought to result from inherited factors (Goggins et al., 1999). Genetic alterations identified to date in invasive pancreatic cancer include activation of K-ras oncogene, overexpression of specific growth factors and their associated factors, and inactivation of the p16, p53, DPC4, BRCA2 and TGF tumor suppressor genes and certain DNA mismatch-repair genes (Goggins et al., 1999, 2000; Moskaluk et al., 1997; Rozeblum et al., 1997). Individuals with mutations or deletion in these genes have an increased risk of developing pancreatic cancer. K-ras gene mutation was the most frequently observed, presenting in early lesions in the pancreatic ducts, and occurring in approximately 90% of patients with pancreatic cancer (Moskaluk et al., 1997). The activation of K-ras oncogene, accordingly, appears nearly to be a prerequisite for the development of pancreatic cancer. Remarkably, Berger et al. showed a higher frequency of K-ras mutations in pancreatic cancer from cigarette smokers (88%) compared with nonsmokers (68%). This would suggest that cigarette smoking plays a role in the development of these mutations (Berger et al., 1999). Molecular epidemiological studies have indicated that polymorphic genes that control the metabolism of carcinogens account for some of the genetic variations in certain tobacco-related cancers such as lung cancer and urinary blabber cancer (Kawajiri et al., 1993). This led Bartsch et al.(Bartsch et al., 1998) to hypothesize that aromatic amines present in tobacco smoking and in cooked food could be involved as causative agents. Based on small samples, they found that the polymorphism of GSTM1 and NAT1 enzymes may be associated with a modest increase in susceptibility to pancreatic cancer. The result requires further confirmatory investigations with much larger samples.

The frequency of point mutation at the 12th codon of c-Ki-ras gene has been examined in Japanese patients with pancreatic cancer. The frequency of point mutations was 75% in one study (Mariyama et al., 1989), while 92% in another study (Nagata et al., 1990). To date, there have been no molecular epidemiological studies conducted in Japan to examine the association of genetic polymorphism with pancreatic cancer risk.

Summary

In Japan, the incidence and mortality of pancreatic cancer have been increasing in the last 4 decades. Rates increase with an advancing age. Both genetic and environmental factors may be playing significant roles in the development of pancreatic cancer. Most consistently described is the increased risk of pancreatic cancer associated with cigarette smoking, but the strength of this association is much less than for lung cancer and other smoking-related cancers. No major risk factor has been established except cigarette smoking. Epidemiological evidence has suggested that long standing diabetes mellitus is associated with an increased risk of pancreatic cancer. It seems reasonable to assume that the high endogenous exposure to insulin may be causative in pancreatic cancer. The increase in the incidence in Japan may possibly be explained by the high smoking rate and the increasing prevalence of diabetics in recent years as well. Much epidemiological works will be warranted to identify and reduce putative exposures.

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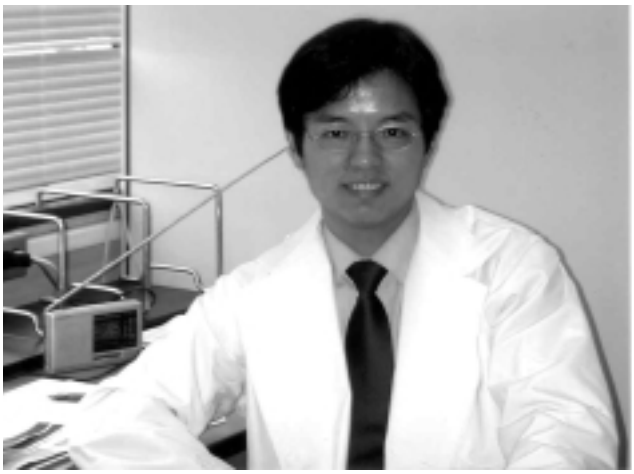

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