Pancreatic Cancer and Factors Associated with the Insulin Resistance Syndrome in the Korean Cancer Prevention Study

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Abstract

There is increasing evidence that type 2 diabetes mellitus and glucose intolerance are a cause, not just a consequence, of pancreatic cancer. We examined whether other factors that characterize the insulin resistance syndrome are also risk factors for pancreatic cancer in a prospective cohort study of 631,172 men and women (ages 45+ years) who received health insurance from the Korean Medical Insurance Corporation. The biennial medical evaluations from 1992 to 1995 provided the baseline information for this study. Relative risks (RR) were estimated using proportional hazards models adjusted for age, sex, smoking, and fasting serum glucose (after excluding the first 2 years of follow-up). There were 2,194 incident cases of pancreatic cancer diagnosed in the cohort over a median follow-up of 12 years. There was no evidence that pancreatic cancer risk was associated with total cholesterol, systolic blood pressure, WBC count, or body mass index. Abnormal levels of aspartate aminotransferase and alanine aminotransferase were both associated with a moderately increased risk of developing the disease (40+ versus <20; RR, 1.33; 95% CI, 1.14-1.55; P_{trend} = 0.05 and RR, 1.34; 95% CI, 1.16-1.56; P_{trend} = 0.02, respectively). Excluding 6 years of follow-up reduced this RR (95% CI) for aspartate aminotransferase to 1.22 (1.01-1.49), but even after excluding 10 years follow-up the RR (95% CI) for alanine aminotransferase was unchanged [1.36 (1.01-1.83)]. Although fasting serum glucose has been found previously to be associated with pancreatic cancer risk in this cohort, most other factors that characterize insulin resistance syndrome were not associated with pancreatic cancer risk. The association with elevated liver enzyme levels is a novel finding that warrants further investigation. (Cancer Epidemiol Biomarkers Prev 2008;17(2):359–64)

Introduction

Insulin resistance syndrome, also known as the metabolic syndrome, is a prediabetic state that produces compensatory hyperinsulinemia and is closely linked to the development of both diabetes and cardiovascular disease (1). Experimental studies have shown that insulin can promote the growth of pancreatic cancer cells (2), and there is increasing epidemiologic evidence that type 2 diabetes mellitus and glucose intolerance are a cause, not just a consequence, of a portion of pancreatic cancers (3-10). Obesity and central adiposity have also been consistently associated with the disease (11-15), but relatively little is known as to whether other, potentially modifiable, risk factors that characterize the insulin resistance syndrome, such as cholesterol levels and blood pressure (16), are also associated with an increased risk of pancreatic cancer.

The Korean Cancer Prevention Study is a long-term prospective study of ~1.3 million Koreans who were insured by the Korean Medial Insurance Corporation, which is now part of the National Health Insurance Corporation. Elevated fasting serum glucose has been found previously to be associated with an increased risk of pancreatic cancer in this cohort, with levels of ≥126 mg/dL associated with a 1.5- to 2-fold increased risk of disease compared with normal levels (17). In the current study, we investigated in detail whether other factors that characterize the insulin resistance syndrome are independently related to the risk of developing pancreatic cancer.

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Materials and Methods

Study Population. The study design and methods for the Korean Cancer Prevention Study have been described in detail previously (17, 18). Briefly, the cohort consists of 1,329,525 Korean civil servants and their dependents (846,907 men and 482,618 women) who received health insurance from the Korean Medial Insurance Corporation and who participated in at least one routine

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biennial medial evaluation between 1992 and 1995. The first of these medical evaluations during this period was considered to be the baseline visit for the study. The population for the current study was restricted to participants who were ages 45+ years at their baseline visit (n = 703,947). Of these participants, 295,717 (42%) were enrolled in 1992, 316,553 (45%) in 1993, 26,789 (4%) in 1994, and 64,879 (9%) in 1995. Participants who reported having atherosclerotic cardiovascular disease, cancer, liver disease, or respiratory disease at or before the baseline visit (n = 47,319) were excluded. In addition, subjects with extremely low body mass index (BMI; <16 kg/m^2) or short stature (≤1.3 m) were also excluded. The first 2 years of follow-up were excluded to reduce the possible effect of unidentified preexisting disease at baseline. Therefore, the current analysis included 631,172 subjects.

Because the study involved routinely collected data, consent was not specifically obtained. The study was approved by the institutional review boards of Yonsei University and the Johns Hopkins Bloomberg School of Public Health.

Data Collection. The biennial medical examinations were conducted by medical staff at local hospitals, following a standard procedure. These routine examinations include measurement of blood pressure (taken while seated) and weight and height measurement (wearing light clothing). Blood samples, taken after an overnight fast, were used to determine total cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and WBC count. Participants also completed a short lifestyle questionnaire. Quality-control procedures were in accordance with the Korean Association of Laboratory Quality Control.

Follow-up and Outcome Classification. Participants were followed from study entry (1992-1995) until first pancreatic cancer diagnosis, death, or the end of the follow-up period (December 31, 2005). Outcomes of cancer incidence were based on national cancer registry data and hospitalization records. Although Korea has a national cancer registry, it did not cover the entire population during the period of follow-up, so claims data for the Korean National Health Insurance Corporation generated from hospital admission files were also used to identify incident cases of pancreatic cancer. Since 2003, this system has also become the main data source for the Korean Central Cancer Registry. An incident cancer case was coded as occurring either on a positive report from the national cancer registry or on a hospital admission for a cancer diagnosis. Outcomes for mortality were ascertained from the causes of death recorded on death certificates. Computerized death certificate searches from the National Statistical Office were done using the national identification number assigned at birth. Trained abstractors coded causes of death according to the *International Classification of Diseases, Tenth Revision*.

Statistical Analysis. We estimated relative risks (RR) and 95% confidence intervals (95% CI) for pancreatic cancer for the baseline risk factors (19) using relative hazards calculated using the Cox proportional hazards model. BMI was calculated as weight divided by height squared, and the normal range was based on the Asian specific cut-point (<18.5, 18.5-22.9, 23.0-27.4, and 27.5+ kg/m^2; ref. 20). Subjects were categorized according to sex-specific quintiles of height, weight, and WBC count and according to categories of ALT, AST, systolic blood pressure (SBP), and total cholesterol that were defined using standard clinical cut-points. All analyses were adjusted for age at enrollment, gender, smoking status [never, past, current (<10, 10-19, and 20+ cigarettes per day)], BMI, and fasting serum glucose levels. Trend tests were conducted using the category medians as the scores. All analyses were conducted using SAS version 8.0 (21).

Results

The cohort included 631,172 participants ages 45+ years at study entry who were followed up for a total of 7,338,797 person-years with a median follow-up of 12.0 years. The median age at baseline was 54 years for males and 56 years for females. Males were much more likely to be current smokers (54.8%) than females (6.2%) and also more likely to drink alcohol (71.3% and 13.4%, respectively; Table 1). During the follow-up period, there were a total of 2,194 incident cases or deaths from pancreatic cancer. Of these, 1,944 were ascertained through the cancer registry or hospital admissions (incident cases) and 250 were ascertained only from death certificates (1,422 of the incident cases were also subsequently reported on death certificates). Median age

Table 1. Baseline characteristics of the subjects in the Korean Cancer Prevention Study (ages 45+ years)

Variable	Men		Women	
	n	Mean (SD), median	n	Mean (SD), median
Age (y)	358,474	54.8 (7.6), 54.0	272,698	57.0 (8.6), 56.0
BMI (kg/m^2)	358,474	23.3 (2.6), 23.2	272,698	24.0 (3.1), 23.8
Fasting serum glucose (mg/dL)	358,244	96.4 (30.0), 91.0	272,464	93.5 (27.6), 89.0
Total cholesterol (mg/dL)	358,243	195.6 (38.8), 193.0	272,470	203.1 (39.8), 200.0
SBP (mm Hg)	358,411	128.5 (18.1), 130.0	272,587	126.4 (20.6), 120.0
ALT	358,220	25.4 (19.0), 21.0	272,444	20.7 (12.0), 18.0
		%		%
Current smoking	358,474	54.8	272,698	6.2
Alcohol drinking	358,474	71.3	272,698	13.4
Family history of diabetes	288,922	4.7	212,232	6.3

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Table 2. Baseline characteristics according to baseline levels of fasting serum glucose

Variable	Fasting serum glucose (mg/dL)						
	<90		90-125		126+		P*
	n	Mean (SD)	n	Mean (SD)	N	Mean (SD)	
Age (y)	308,380	55.5 (8.1)	282,528	55.9 (8.1)	40,264	57.3 (8.0)	<0.0001
BMI (kg/m^2)	308,380	23.4 (2.8)	282,528	23.7 (2.9)	40,264	24.0 (2.9)	<0.0001
Total cholesterol (mg/dL)	307,928	195.3 (37.7)	282,525	201.1 (39.4)	40,260	209.7 (47.9)	<0.0001
SBP (mm Hg)	308,304	125.7 (18.7)	282,443	128.9 (19.5)	40,251	132.8 (20.4)	<0.0001
ALT	307,908	22.1 (14.8)	282,497	24.1 (16.8)	40,259	28.1 (23.9)	<0.0001
		%		%		%	
Current smoking	308,380	33.1	282,528	34.1	40,264	37.0	<0.0001
Alcohol drinking	308,380	43.2	282,528	49.0	40,264	51.0	<0.0001
Family history of diabetes	245,298	4.4	223,759	5.2	32,097	14.6	<0.0001

*Tested using ANOVA for continuous variables and χ^2 test for categorical variables.

at diagnosis/death was 57 years for males (n = 1,505) and 61 years for females (n = 689). Analyses were initially done separately for pancreatic cancer incidence and mortality. However, the results were generally similar because the high fatality rate of pancreatic cancer meant that mortality was a close approximation to incidence; therefore, we report only the results for the combined outcome.

In this cohort, elevated fasting serum glucose levels were strongly associated with several factors, including BMI, total cholesterol, blood pressure, and ALT (P < 0.001; Table 2). Current smokers, alcohol drinkers, and those with a family history of diabetes were also more likely to have elevated fasting serum glucose levels (P < 0.001).

There was no clear relationship between total cholesterol level, SBP, or WBC count and pancreatic cancer risk. However, elevated levels of AST and ALT were associated with a moderately increased risk of developing the disease. For abnormal (40+) versus normal (<20) liver function levels, the RR (95% CI) for pancreatic cancer was 1.33 (1.14-1.55) for AST and 1.34 (1.16-1.56) for ALT (P_{trend} = 0.05 and 0.02, respectively; Table 3).

To assess whether this association could be due to reverse causality, we examined the effect of excluding increasing periods of follow-up (4, 6, 8, and 10 years; Table 4). There was a small reduction in the RR (95% CI) for AST when 6 years of follow-up were excluded [1.22 (1.01-1.49); P_{trend} = 0.04 for 40+ versus 20]. For ALT, the patterns of risk were largely unchanged even after exclusion of the first 10 years of follow-up, although the reduction in the number of cases decreased the power. Tests for interaction between AST or ALT levels and follow-up time were not statistically significant (P = 0.99 and 0.93, respectively, treating both variables as continuous).

ALT and AST levels in this cohort were highly correlated (r = 0.73) and both were associated with alcohol consumption and hepatitis B virus infection and in those who were nondrinkers with obesity and elevated fasting serum glucose levels (data not shown). However, neither alcohol consumption (RR, 1.06; 95% CI, 0.83-1.34 for 50+ versus 0 g/d; P_{trend} = 0.2) nor hepatitis B surface antigen status was associated with pancreatic cancer risk (RR, 1.13; 95% CI, 0.84-1.52). In the subset of subjects who were not hepatitis B surface antigen carriers and who reported that they did not drink alcohol, the RRs (95% CIs) were higher for both abnormal (40+) ALT [1.62 (0.98-2.68)] and AST [1.97 (1.13-3.45)]. Hepatitis B surface antigen status information was only available for a subset

Table 3. RR (95% CI) of pancreatic cancer according to available clinical measurements

	Cases	RR (95% CI)	
		Adjusted*	Adjusted †
Total cholesterol (mg/dL)			
<200	1,232	1.0	1.0
200-239	647	0.91 (0.83-1.01)	0.91 (0.82-1.00)
240+	311	1.00 (0.88-1.13)	0.97 (0.85-1.10)
P_{trend}		0.98	0.77
SBP (mm Hg)			
<120	530	1.0	1.0
120-129	487	0.97 (0.86-1.10)	0.97 (0.86-1.10)
130-139	467	1.01 (0.89-1.14)	1.01 (0.89-1.14)
140+	710	0.99 (0.88-1.11)	0.98 (0.88-1.10)
P_{trend}		0.91	0.98
WBC‡ (cells/L)			
1st	226	1.0	1.0
2nd	252	1.07 (0.92-1.24)	1.08 (0.93-1.26)
3rd	213	0.97 (0.83-1.14)	0.98 (0.83-1.14)
4th	265	1.12 (0.97-1.30)	1.11 (0.96-1.29)
5th	262	1.08 (0.93-1.26)	1.05 (0.91-1.22)
P_{trend}		0.33	0.58
AST			
<20	578	1.0	1.0
20-30	976	0.99 (0.89-1.10)	1.00 (0.90-1.11)
30-40	412	1.18 (1.04-1.34)	1.19 (1.05-1.35)
40+	224	1.34 (1.15-1.56)	1.33 (1.14-1.55)
P_{trend}		0.06	0.05
ALT			
<20	975	1.0	1.0
20-30	708	1.05 (0.96-1.16)	1.06 (0.96-1.16)
30-40	273	1.19 (1.04-1.36)	1.19 (1.04-1.36)
40+	234	1.36 (1.18-1.57)	1.34 (1.16-1.56)
P_{trend}		0.02	0.02

*Adjusted for age and gender.
† Adjusted for age, gender, body mass index, smoking, and fasting serum glucose levels.
‡ Sex-specific quintiles WBC: male (<5,700, 5,700-6,599, 6,600-7,399, 7,400-8,499, and ≥8,500) and female (<5,200, 5,200-5,999, 6,000-6,699, 6,700-7,699, and ≥7,700).

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Table 4. RR (95% CI) of pancreatic cancer according to ALT and AST levels excluding 2, 4, 6, 8, and 10 years of follow-up

	No. years of follow-up excluded									
	2		4		6		8		10	
	Cases	RR* (95% CI)	Cases	RR* (95% CI)	Cases	RR* (95% CI)	Cases	RR* (95% CI)	Cases	RR* (95% CI)
AST										
<20	578	1.00	494	1.00	392	1.00	276	1.00	137	1.00
20-30	976	1.00 (0.90-1.11)	847	1.02 (0.91-1.14)	669	1.02 (0.90-1.16)	460	1.00 (0.86-1.16)	245	1.09 (0.88-1.34)
30-40	412	1.19 (1.05-1.35)	336	1.14 (0.99-1.31)	258	1.11 (0.95-1.31)	175	1.08 (0.89-1.31)	832	1.04 (0.79-1.37)
40+	224	1.33 (1.14-1.55)	195	1.36 (1.15-1.61)	136	1.22 (1.01-1.49)	89	1.16 (0.91-1.48)	45	1.21 (0.86-1.70)
P_{trend}		0.05		0.06		0.04		0.05		0.17
ALT										
<20	975	1.00	845	1.00	662	1.00	435	1.00	223	1.00
20-30	708	1.06 (0.96-1.16)	602	1.03 (0.92-1.14)	465	1.01 (0.89-1.13)	332	1.08 (0.94-1.25)	166	1.01 (0.83-1.24)
30-40	273	1.19 (1.04-1.36)	225	1.12 (0.96-1.30)	174	1.09 (0.92-1.29)	126	1.19 (0.97-1.45)	63	1.10 (0.83-1.46)
40+	234	1.34 (1.16-1.56)	200	1.31 (1.12-1.54)	154	1.28 (1.07-1.53)	107	1.34 (1.08-1.67)	58	1.36 (1.01-1.83)
P_{trend}	200	0.02		0.06		0.09		0.01		0.10

*Adjusted for age, gender, body mass index, smoking, and fasting serum glucose levels.

of the study population (32%); hence, the power of this analysis was somewhat limited.

There was no clear relationship between increased height, weight, or BMI and the risk of developing pancreatic cancer (Table 5). Neither was there evidence that a family history of diabetes was associated with an increased risk of pancreatic cancer (RR, 1.04; 95% CI, 0.84-1.29).

To evaluate potential effect modification, stratified analyses were conducted for men and women separately. There were no evidence of statistically significant heterogeneity between males and females for any of the risk factors considered ($P > 0.05$). In general, the results were similar to those for all subjects combined, but there was evidence of a weak association between elevated weight and pancreatic cancer risk in females, which was not observed for males (RR, 1.19; 95% CI, 0.93-1.51; $P_{trend} = 0.01$ versus RR, 0.97; 95% CI, 0.82-1.14; $P_{trend} = 0.9$ for the top compared with the bottom quintile).

We also repeated all of the analyses in the subgroups of never smokers and nondiabetics (defined as no self-reported diabetes at baseline and/or fasting serum glucose <140 mg/dL) to assess whether there may have been residual confounding by these factors. In the analysis restricted to never smokers, there was also some evidence of an association with increasing weight (RR, 1.24; 95% CI, 0.99-1.55 for the top compared with the bottom quintiles; $P_{trend} = 0.04$). There were no material differences observed when the analyses were restricted to nondiabetics, which was consistent with the observation that adjustment for fasting serum glucose levels did not modify any of the associations.

Discussion

In this large, prospective study, pancreatic cancer risk was associated with abnormal ALT and AST levels. Despite the fact that cholesterol, SBP, and BMI were strongly associated with fasting serum glucose levels, there was no evidence that these factors were associated with pancreatic cancer risk.

As far as we are aware, this is the first study to examine the association between liver enzymes and pancreatic cancer risk. The moderate association with ALT was not altered materially when increasing lag periods were considered, which suggests that the association was not due to reverse causality. The association with AST was weakened slightly when 6+ years of follow-up were excluded. Factors that were related to elevated ALT and AST in this population were fasting serum glucose, obesity, alcohol consumption, and hepatitis B virus infection. However, most of these factors were not related to pancreatic cancer in this cohort and adjustment for fasting serum glucose levels did not materially alter the estimated RRs. Liver enzymes are not

Table 5. RR (95% CI) of pancreatic cancer according to anthropometric factors

	Cases	RR (95% CI)	
		Adjusted*	Adjusted †
Height (cm) ‡			
1st	414	1.0	1.0
2nd	355	0.93 (0.80-1.07)	0.92 (0.80-1.07)
3rd	497	1.13 (0.99-1.29)	1.12 (0.98-1.28)
4th	443	1.03 (0.89-1.18)	1.02 (0.89-1.18)
5th	485	1.09 (0.94-1.25)	1.09 (0.94-1.25)
P_{trend}		0.33	0.33
Weight (kg) §			
1st	456	1.0	1.0
2nd	397	0.92 (0.81-1.06)	0.93 (0.81-1.07)
3rd	486	1.04 (0.92-1.19)	1.07 (0.93-1.22)
4th	400	0.99 (0.86-1.14)	1.01 (0.88-1.17)
5th	455	1.01 (0.88-1.16)	1.04 (0.90-1.19)
P_{trend}		0.59	0.42
BMI (kg/m^2)			
<18.5	66	0.76 (0.59-0.98)	0.78 (0.60-1.00)
18.5-22.9	963	1.0 (Reference)	1.0 (Reference)
23.0-27.4	1,008	0.98 (0.90-1.08)	0.98 (0.89-1.07)
27.5+	157	0.97 (0.82-1.15)	0.95 (0.80-1.12)
P_{trend}		0.30	0.38

*Adjusted for age and gender.
† Adjusted for age, gender, smoking, and fasting serum glucose levels.
‡ Sex-specific quintiles height: male (<162, 162-164.9, 165-167.9, 168-170.9, and ≥171) and female (<148, 148-151.9, 152-154.9, 155-157.9, and ≥158).
§ Sex-specific quintiles weight: male (<57, 57-61.9, 62-66.4, 66.5-71.9, and ≥72) and female (<49, 49-53.9, 54-57.9, 58-62.9, ≥63).

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formally classified as components of the insulin resistance syndrome, but there is increasing evidence that they are also associated with insulin resistance (22-24). In addition to the association with insulin resistance, these enzymes are elevated in individuals with pancreatitis, a risk factor for pancreatic cancer, and among those with bile duct obstruction. It is possible that these enzymes may be elevated in response to preneoplastic changes in the pancreas. For example, chronic pancreatitis-like changes have been observed in conjunction with pancreatic intraepithelial neoplasia lesions in patients at high risk of developing pancreatic cancer (25), and pancreatic intraepithelial neoplasia lesions are more frequent in individuals with chronic pancreatitis (26). As well as examining this association in other study populations, studies are needed to determine possible causes of the abnormal liver function before the development of invasive pancreatic cancer.

Obesity, defined as BMI >27.5 kg/m^2, was not related to pancreatic cancer risk in this cohort. Most definitions of the insulin resistance syndrome are based on measures of central adiposity, such as waist circumference, rather than the overall obesity measure of BMI (16). Unfortunately, neither waist nor hip circumference measures were available in the current study. Several previous studies, including a pooled analysis of Asian cohorts, have found that there may be a stronger association between pancreatic cancer risk and waist circumference than with BMI (12-15).

Several other studies have also reported null associations between blood pressure, cholesterol, and the risk of pancreatic cancer (15, 27, 28). One cohort study of hypertensive patients reported an increased risk of developing pancreatic cancer for women compared with the risk in the general population (29).

This is one of the largest prospective studies of pancreatic cancer to date. The availability of various clinical measures, including cholesterol, blood pressure, and liver enzyme levels, enabled the evaluation of several novel risk factors for a disease with few established causes. Adjustment for fasting serum glucose levels, as opposed to self-reported diabetes, is an advantage in that the potential for residual confounding with respect to preclinical diabetes is reduced and there is unlikely to be nondifferential misclassification of diabetes status. It also allowed us to assess whether any other factors that were associated with fasting serum glucose levels were independently associated with pancreatic cancer risk. A potential limitation of this study is that there could be additional assay variability because all the measurements were collected for routine clinical, not for research, purposes and measurements for the entire cohort were only available at baseline. However, quality-control procedures were followed, which helped to ensure reliability of the assays. Furthermore, the use of clinical samples makes these findings readily generalizable to the clinic setting. The large size of the cohort meant that it was not possible to conduct active follow-up; hence, information on emigration was not available and we were unable to assess the losses to follow-up. However, emigration is thought to be limited in this population and, if present, is nondifferential with respect to pancreatic cancer.

The disease incidence rates reported in a previous study of this cohort of ~20 per 100,000 were of similar magnitude to the rates for South Korea reported in *Cancer Incidence in Five Continents* (30). Microscopic confirmation of pancreatic cancer was not available and it is possible that there was some misclassification of the outcome (31). One recent study found that the association with BMI was limited to microscopically confirmed cases of pancreatic cancer (32), which suggests that misclassification was nondifferential. Whether misclassification would be nondifferential in other study populations is difficult to predict and could vary according to the risk factor of interest and the diseases that were misclassified as pancreatic cancer.

Although fasting serum glucose has been found previously to be associated with pancreatic cancer risk in this cohort, most other factors that characterize insulin resistance syndrome were not associated with pancreatic cancer risk. The association with elevated liver enzyme levels is a novel finding that warrants further investigation.

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