The Effect of Modifiable Risk Factors on Pancreatic Cancer Mortality in Populations of the Asia-Pacific Region

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Abstract

Background: Pancreatic cancer accounts for about 220,000 deaths each year. Known risk factors are smoking and type 2 diabetes. It remains to be seen whether these risk factors are equally important in Asia and whether other modifiable risk factors have important associations with pancreatic cancer.

Methods: An individual participant data analysis of 30 cohort studies was carried out, involving 420,310 Asian participants (33% female) and 99,333 from Australia/New Zealand (45% female). Cox proportional hazard models, stratified by study and sex and adjusted for age, were used to quantify risk factors for death from pancreatic cancer.

Results: During 3,558,733 person-years of follow-up, there were 534 deaths from pancreatic cancer (54% Asia and 33% female). Mortality rates (per 100,000 person-years) from pancreatic cancer were 10 for men and 8 for women. The following are age-adjusted hazard ratios (95% confidence interval) for death from pancreatic cancer: for current smoking, 1.61 (1.12-2.32); for diabetes, 1.76 (1.15-2.69); for a 2-cm increase in waist circumference, 1.08 (1.02-1.14). All three relationships remained significant (P < 0.05) after adjustment for other risk factors. There was no evidence of heterogeneity in the strength of these associations between either cohorts from Asia and Australia/New Zealand or between the sexes. In men, the combination of cigarette smoking and diabetes more than doubled the likelihood of pancreatic cancer (2.47; 95% confidence interval, 1.17-5.21) in both regions.

Conclusions: Smoking, obesity, and diabetes are important and are potentially modifiable risk factors for pancreatic cancer in populations of the Asia-Pacific region. Activities to prevent them can be expected to lead to a major reduction in the number of deaths from this cancer, particularly in Asia with its enormous population. (Cancer Epidemiol Biomarkers Prev 2006;15(12):2435–40)

Introduction

Worldwide, pancreatic cancer accounts for about 220,000 deaths annually and is the sixth major cause of cancer-related mortality due to its very low 5-year survival; <5% in some instances (1, 2). Increasing age is strongly associated with elevations in the risk of pancreatic cancer, with <10% of cases occurring in individuals <50 years of age (2). Modifiable conditions, such as cigarette smoking, which is suggested to explain one quarter of cases (3), and type 2 diabetes (4), are widely accepted as risk factors for pancreatic cancer. However, it is unclear whether other factors may also have important associations with the disease. For example, some studies have found obesity to be a risk factor independent of its effects on diabetes (4-6). In addition, a recent meta-analysis (7) of prospective cohorts concluded that there was a positive, but weak, association between body mass index (BMI) and pancreatic cancer risk, such that a 1-unit increment in BMI was associated with a 2% increase in risk of pancreatic cancer. There is also a small body of literature suggesting associations between both blood pressure (8-10) and cholesterol (11-13) with the risk of cancer.

To date, most of the prospective studies that have investigated the environmental and physiologic determinants of pancreatic cancer have been conducted in American (6) or European (5) populations. By comparison, there are relatively few studies examining the role of putative risk factors in the etiology of the disease in Asian populations (14). This is of importance given the recent substantial increases in the prevalence of cigarette smoking (15), type 2 diabetes (16), and obesity (17) in this highly populous region.

The Asia Pacific Cohort Studies Collaboration (18) comprises a large number of prospective cohort studies in the region and was established to provide reliable evidence about the relationships between a variety of modifiable risk factors and the incidence of major causes of death among populations in this region. The aims of this study were 2-fold: (a) to investigate the associations between putative risk factors and the risk of pancreatic cancer and (b) to estimate the burden of the disease due to any important and modifiable risk factor in two ethnically diverse populations of the Asia-Pacific Region, China, and Australia.

Materials and Methods

Details of study identification, data collection, and event verification in the Asia Pacific Cohort Studies Collaboration are described elsewhere (18-24). Briefly, studies were included if they had continued follow-up for at least 5,000 person-years and had recorded vital status at the end of follow-up. Studies were excluded if entry was dependent upon a particular condition or risk factor. Mortality was classified according to the 9th Revision of the International Classification of Diseases: Pancreatic cancer was selected as ICD 157. Studies were...
classified as Asian if their participants were recruited from Mainland China, Hong Kong, Japan, Korea, Singapore, Taiwan, or Thailand and Australia/New Zealand (ANZ) if from Australia or New Zealand.

All data on cigarette smoking (19) were based on self-report at the time of entry into one of the included studies; smoking status was recorded as current, former, or never smoker. Eighteen studies additionally recorded the average number of cigarettes per day for smokers; groups of <20 and ≥20 cigarettes were chosen as 20 cigarettes correspond to one standard pack.

Within most studies in the Asia Pacific Cohort Studies Collaboration, there was no differentiation made between type 1 and type 2 diabetes; hence, the analyses included all individuals with diabetes recorded at study baseline based on either self-report (20) or an oral glucose tolerance test (ref. 21; 86% of the total study population), or both. Using the values for height and weight measured at study baseline, BMI (22) was computed as weight in kilograms divided by height squared (kg/m²). Some studies additionally recorded waist circumference (cm). At recruitment, data were also collected on current medications and several risk factors, including blood pressure (23) and cholesterol (24).

Analyses used individual participant data and were restricted to individuals ages ≥20 years at enrollment. Cox proportional hazard models, stratified by study and sex and adjusted for age, were used to estimate hazard ratios (HR) and 95% confidence interval (95% CI) associated with putative risk factors both before and after adjustment for other risk factors. Associations between continuously distributed variables and pancreatic cancer were assessed by obtaining the HRs and 95% CIs for a standard increment in each variable. Dose-response associations were explored by categorizing study participants into equal tertiles of continuous distributions. Due to the limited number of events among the studies that had information on waist circumference, we did not examine the dose-response association between waist circumference and pancreatic cancer but instead examined the relationship with waist circumference as a continuous variable. Tests for regional and sex interactions were conducted by adding interaction terms to the Cox model.

Within prospective cohorts, values for risk factors measured at study baseline will fluctuate due to several factors, including measurement error or within-person variability, resulting in an underestimation of the true association with disease risk, which is termed regression dilution bias (25). By using repeat measurements of the risk factors from a sample of the total study population, attenuation coefficients were derived using a linear regression model that accounted for the heterogeneity of variance between studies, within-subject correlation, and the varying time intervals between measurements (25). Information on repeat measures of blood pressure, total cholesterol, BMI, waist circumference, and fasting glucose were available on up to 16 studies for between one to seven occasions with a median between 3 and 29 years after the baseline measurement. Regression attenuation coefficients were calculated in this way for total cholesterol (1.7), systolic blood pressure (1.9), diastolic blood pressure (2.1), fasting glucose (1.6), BMI (1.2), and waist circumference (1.4).

The excess risk of pancreatic cancer associated with being a current smoker and having diabetes was examined by creating dummy variables in a multivariate model and testing for effect modification by introducing interaction terms. The population attributable risks for mortality from pancreatic cancer associated with risk factors were calculated separately for Australia and China, using previously published prevalence estimates of the prevalence of smoking (15, 26) and type 2 diabetes (27, 28) and the formula:

\[
\text{PAR} = \frac{P(RR - 1)}{1 + P(RR - 1)}.
\]

**Results**

The characteristics of the participants in the 30 cohort studies within the Asia Pacific Cohort Studies Collaboration that contributed to these analyses are summarized in Table 1. In total, 182,173 (35% female) individuals with a median follow-up of 6.9 years and a mean age of 47 years were included in the analysis. The mean prevalence of diabetes was similar among cohorts from Asia and ANZ (6.6% and 5%, respectively), whereas the prevalence of current smoking and mean BMI varied substantially within, and between, the two regions (Table 1).

Overall, there were 324 deaths from pancreatic cancer (54% Asia and 33% female) during 3,558,733 person-years of follow-up, although the actual number of deaths included in each analysis of risk factors varied according to the availability of information for each risk factor (Table 2). In both Asia and ANZ, mortality rates from pancreatic cancer were higher in men than in women (7 versus 5 per 100,000 person-years among men and women in Asia, respectively); in ANZ, the corresponding rates were 19 and 13 per 100,000 person-years, respectively. Statistical heterogeneity by sex and region was examined by adding interaction terms for sex and region in the Cox model.

**Age and Pancreatic Cancer.** The risk of pancreatic cancer was strongly associated with age. Among individuals over the age of 75 years, the risk of developing the neoplasm was 14 times higher compared with those <55 years of age (HR, 13.9; 95% CI, 7.06-27.4). The association was approximately linear in that for every extra 10 years of increase in age, the risk of pancreatic cancer more than doubled (HR, 2.55; 95% CI, 2.16-2.97). There was no evidence of heterogeneity in the strength of the association between men and women or between Asia and ANZ cohorts (P > 0.8 for both).

**Cigarette Smoking and Pancreatic Cancer.** In age-adjusted analyses, after exclusion of former smokers, current smokers had a 60% increased risk of pancreatic cancer compared with never smokers (HR, 1.61; 95% CI, 1.12-2.32), which was unaffected by adjustment for diabetes and BMI. There was good evidence of a dose-response association (Table 2) such that for every five cigarettes smoked per day, the risk of mortality from pancreatic cancer increased by 10% (P = 0.03; Fig. 1). There was no difference in the strength of the association between Asia and ANZ cohorts (P = 0.94) or between men and women (P = 0.14).

**Blood Glucose, Diabetes, and Pancreatic Cancer.** Individuals with diabetes had a 75% greater risk of pancreatic cancer compared with individuals without diabetes (HR, 1.76; 95% CI, 1.15-2.69), which remained largely unchanged after adjustment for smoking and BMI (HR, 1.78; 95% CI, 1.16-2.73). There was no evidence of any regional or sex differences in the strength of the observed relationship (P > 0.3 for both). To preclude the possibility of reverse causality (i.e., pancreatic cancer causing diabetes), the analyses were repeated after excluding the first 5 years of follow-up, which resulted in little change in the HR (HR, 1.75; 95% CI, 0.87-3.55). Based on a small subgroup of individuals with information on blood glucose, there was a statistically significant dose-response relationship between blood glucose and the risk of pancreatic cancer such that a 1 mmol/L higher blood glucose was associated with an 11% greater risk of mortality from pancreatic cancer (Fig. 1).

**Body Anthropometry and Pancreatic Cancer.** BMI was not associated with mortality from pancreatic cancer in this cohort (Fig. 1), but there was some evidence of a positive association with central obesity, such that a 2-cm higher waist circumference was associated with an 8% (95% CI, 2.15%) greater risk of pancreatic cancer. The association was independent of the potential confounding effects of diabetes and smoking, with no
Although the association between total cholesterol and mortality from pancreatic cancer was not statistically significant \((P=0.29)\), examination of the dose-response relationship suggests a weak inverse relationship between total cholesterol and risk of pancreatic cancer: individuals in the top tertile of blood cholesterol had about a 25% lower risk of mortality from pancreatic cancer than those in the lowest tertile (Table 2). Because of the possibility of reverse causality, we excluded those individuals who died from pancreatic cancer within the first 5 years of follow-up, but it had no material effect on the association. We also found no evidence of regional or sex differences in the strength of the associations \((P>0.4\) for both). 

### Total Cholesterol and Pancreatic Cancer

Although the association between total cholesterol and mortality from pancreatic cancer was not statistically significant \((P=0.29)\), examination of the dose-response relationship suggests a weak inverse relationship between total cholesterol and risk of pancreatic cancer: individuals in the top tertile of blood cholesterol had about a 25% lower risk of mortality from pancreatic cancer than those in the lowest tertile (Table 2). Because of the possibility of reverse causality, we excluded those individuals who died from pancreatic cancer within the first 5 years of follow-up, but it had no material effect on the association. We also found no evidence of regional or sex differences in the strength of the associations \((P>0.4\) for both).

### Blood Pressure, Antihypertensive Medication, and Pancreatic Cancer

There was no evidence of an association between blood pressure and pancreatic cancer (Fig. 1). Based on a subsample of individuals, among whom there were 130 deaths, a borderline statistically significant positive association was observed between the use of antihypertensive medication and mortality from pancreatic cancer. Individuals who were receiving blood pressure lowering treatment at study baseline had a 50% greater risk compared with those who were not on antihypertensive treatment (HR, 1.46; 95% CI, 0.98-2.19). This association was little altered by adjustment for cigarette smoking, BMI, diabetes, or blood pressure. There was no evidence of heterogeneity between regions or by sex \((P>0.10\) for both).

### Contribution of Modifiable Risk Factors to Mortality from Pancreatic Cancer

In the current analyses, the combination of cigarette smoking and diabetes more than doubled the likelihood of mortality from pancreatic cancer in both regions (HR, 2.47; 95% CI, 1.17-5.21). The contribution of cigarette smoking and diabetes to mortality from pancreatic cancer differed substantially between the sexes and between China and Australia, assuming cause and effect (Table 3).

### Discussion

The present study confirms the important etiologic role of cigarette smoking and diabetes in pancreatic cancer found in Western populations and extends these findings to Asian populations. Moreover, it provides some support for central obesity, as opposed to BMI, being an independent risk factor for the disease. The principal strengths of the current study are its large amount of individual participant data, over three quarters of which are derived from Asian populations, and its prospective design, and that more than three quarters of the data included in the analyses are derived from Asian populations, where data on risk factors for pancreatic cancer are more limited.

As with previous studies (29-32), we observed a significant dose-response relationship between cigarette smoking and pancreatic cancer. We were unable to exclude the possibility of...
residual confounding by consumption of alcohol due to a lack of information on alcohol intake within the Asia Pacific Cohort Studies Collaboration. However, several prospective studies have reported that adjustment for alcohol did not materially attenuate the association between smoking and pancreatic cancer (4,32).

A relationship between type 2 diabetes and mortality from pancreatic cancer has been consistently reported in the literature. The current finding of an approximate 80% increase in risk is in line with findings from a recent meta-analysis that concluded that type 2 diabetes is associated with an ~2-fold increase in risk of the neoplasm (3). Further support for a causal association between diabetes and mortality from pancreatic cancer is provided by evidence of a dose-response association in the current study that is supported by findings from other large prospective studies (33-35).

Table 2. HRs and 95% CIs for the associations between known and putative risk factors and mortality from pancreatic cancer

<table>
<thead>
<tr>
<th>Covariate</th>
<th>No. subjects</th>
<th>No. deaths</th>
<th>Adjusted for age, sex and study HR (95% CI)</th>
<th>Multiple-adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarettes per day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoking*</td>
<td>59,387</td>
<td>84</td>
<td>1</td>
<td>1†</td>
</tr>
<tr>
<td>&lt;20</td>
<td>8,690</td>
<td>14</td>
<td>1.17 (0.64-2.13)</td>
<td>1.17 (0.64-2.13)</td>
</tr>
<tr>
<td>≥20</td>
<td>9,242</td>
<td>26</td>
<td>1.86 (1.09-3.17)</td>
<td>1.86 (1.09-3.17)</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.2*</td>
<td>125,855</td>
<td>28</td>
<td>1</td>
<td>1†</td>
</tr>
<tr>
<td>5.2-5.78</td>
<td>41,118</td>
<td>28</td>
<td>1.75 (1.01-3.04)</td>
<td>1.79 (1.03-3.10)</td>
</tr>
<tr>
<td>≥5.79</td>
<td>27,041</td>
<td>29</td>
<td>1.96 (1.12-3.44)</td>
<td>2.08 (1.18-3.67)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;23*</td>
<td>121,714</td>
<td>77</td>
<td>1</td>
<td>1†</td>
</tr>
<tr>
<td>23-26</td>
<td>110,408</td>
<td>76</td>
<td>1.03 (0.74-1.45)</td>
<td>1.07 (0.76-1.49)</td>
</tr>
<tr>
<td>≥26</td>
<td>74,093</td>
<td>77</td>
<td>0.98 (0.68-1.42)</td>
<td>1.00 (0.69-1.45)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;159*</td>
<td>84,806</td>
<td>73</td>
<td>1</td>
<td>1†</td>
</tr>
<tr>
<td>160-170</td>
<td>142,524</td>
<td>74</td>
<td>0.71 (0.48-1.06)</td>
<td>0.71 (0.48-1.06)</td>
</tr>
<tr>
<td>≥171</td>
<td>74,568</td>
<td>69</td>
<td>1.17 (0.71-1.93)</td>
<td>1.21 (0.74-1.98)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4.8*</td>
<td>105,749</td>
<td>68</td>
<td>1</td>
<td>1†</td>
</tr>
<tr>
<td>4.8-5.7</td>
<td>108,609</td>
<td>72</td>
<td>0.87 (0.61-1.22)</td>
<td>0.87 (0.61-1.23)</td>
</tr>
<tr>
<td>≥5.8</td>
<td>69,465</td>
<td>68</td>
<td>0.74 (0.50-1.08)</td>
<td>0.73 (0.50-1.07)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;130*</td>
<td>200,311</td>
<td>81</td>
<td>1</td>
<td>1†</td>
</tr>
<tr>
<td>131-146</td>
<td>59,993</td>
<td>70</td>
<td>1.33 (0.95-1.86)</td>
<td>1.34 (0.96-1.87)</td>
</tr>
<tr>
<td>≥147</td>
<td>46,807</td>
<td>79</td>
<td>1.19 (0.84-1.69)</td>
<td>1.20 (0.84-1.71)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;76*</td>
<td>129,210</td>
<td>82</td>
<td>1</td>
<td>1†</td>
</tr>
<tr>
<td>76-86</td>
<td>107,068</td>
<td>74</td>
<td>0.85 (0.61-1.17)</td>
<td>0.85 (0.62-1.18)</td>
</tr>
<tr>
<td>≥87</td>
<td>69,933</td>
<td>74</td>
<td>0.94 (0.67-1.31)</td>
<td>0.95 (0.68-1.33)</td>
</tr>
</tbody>
</table>

*Reference group.
†Adjusted for diabetes and BMI.
‡Adjusted for smoking and BMI.
§Adjusted for smoking and diabetes.
‖Adjusted for smoking, diabetes and BMI.
In a recent meta-analysis, obesity was weakly associated with an increased risk of pancreatic cancer (7), but findings from the current study for such an association were unequivocally null. BMI, however, is a crude measure of adiposity and provides no information regarding the distribution of body fat, which may be more predictive of risk. Central adiposity is strongly correlated with intra-abdominal fat and with increased insulin secretion and insulin resistance. Such disturbances in insulin metabolism are suggested to have a carcinogenic effect (36). In the current study, waist circumference, which is a measure of central obesity, was significantly and positively associated with pancreatic cancer, in agreement with the findings of Larsson et al. (5). Similarly, data from the European Prospective Investigation into Cancer and Nutrition study also reported that, in contrast to BMI that showed no association, central adiposity was positively associated with the incidence of pancreatic cancer (37). Moreover, in the current analyses, the relationship between central adiposity and mortality from pancreatic cancer was not confounded by diabetes; as such, adjustment did not have any material effect on the association. Our finding of a weak positive association between height and pancreatic cancer is in agreement with some (36, 38), but not all (39-41), previous reports. In the European Prospective Investigation into Cancer and Nutrition study, height was shown to be positively associated with pancreatic cancer, although the relationship was driven by a low risk in the lowest quartile of the height distribution (37). Therefore, it remains to be determined whether height is an important risk factor for the neoplasm.

Previous studies have suggested positive associations between hypertension and the use of antihypertensive medication, such as diuretics and calcium-channel blockers in particular, and risk of cancer (42-45). We found no evidence to suggest an association with blood pressure, but there was some evidence to suggest a 50% greater risk of mortality from pancreatic cancer among those prescribed, blood pressure–lowering medications. However, data from large blood pressure–lowering trials, including PROGRESS (46), reported no excess risk of all-cause cancer among individuals prescribed more intensive, versus less intensive, regimes of antihypertensive medication. Moreover, data from ALLHAT (47) showed that calcium channel blockers were not associated with an increased risk of cancer compared with other blood pressure–lowering medications. It is possible that our finding of an increased risk of pancreatic cancer with antihypertensive medication is a chance finding due to bias, particularly survivor bias, that is those individuals not prescribed blood pressure–lowering treatment died from cardiovascular disease before they contracted cancer. Alternatively, it may be an artifact due to the fact that individuals receiving treatment for hypertension may be more likely to have had their pancreatic cancer diagnosed compared with untreated hypertensives who may not have received regular medical check-ups.

The literature contains some reports (11-13) of an inverse relationship between blood cholesterol and increased risk of cancer, specifically of the lung and liver, although data from the current analysis do not lend strong support to this hypothesis in agreement with findings from a large Finnish study that reported no association between either total or high-density lipoprotein cholesterol with pancreatic cancer (48). Moreover, evidence from large randomized trials of cholesterol-lowering agents, such as the Heart Protection Study (49), do not support a greater risk of cancer among subjects receiving cholesterol medication compared with those who do not, although the shorter length of follow-up in such studies (<5 yrs) makes it impossible to examine the long-term effect of treatment. Hence, it remains unclear whether a low cholesterol level is, indeed, a risk factor for certain cancers.

In addition to the lack of information on duration of smoking, age of smoking uptake, and the inability to discriminate between type 1 and type 2 diabetes, all of which may have diluted the strength of the observed associations, there are several other limitations that warrant discussion. The analyses were based on self-reported cigarette consumption, which may have introduced bias. In addition, measurement error may have been present especially for waist circumference, which is more difficult to reliably measure than either weight or height. Finally, the individual studies used different methods to verify mortality from pancreatic cancer, whereas the methods used will also have varied over time. The lack of standardization could have had some unpredictable effect on the results.

To our knowledge, this is the first study to evaluate the population attributable risks of smoking and diabetes on mortality from pancreatic cancer among men from two populations of the Asia-Pacific region. The coexistence of these two modifiable risk factors conferred a more than doubling of risk of mortality from pancreatic cancer compared with men in whom such risk factors were absent. Cigarette smoking and diabetes explained a significant proportion of pancreatic cancer in both China and Australian, which suggests that interventions that reduce the prevalence of smoking and diabetes, together with those targeting obesity, would have a substantial effect on reducing mortality from a wide spectrum of chronic diseases, including pancreatic cancer in both Asian and non-Asian populations.

Table 3. Population attributable fractions for mortality from pancreatic cancer due to cigarette smoking and diabetes in China and Australia

<table>
<thead>
<tr>
<th></th>
<th>China</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
1. Reference 1.


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