Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts

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We examined the associations of body mass index (BMI), waist circumference, a history of diabetes, and cigarette smoking with risk of pancreatic cancer among 37 147 women and 45 906 men followed up during 560 666 person-years in the Swedish Mammography Cohort and the Cohort of Swedish Men; 136 incident cases of pancreatic cancer were diagnosed. The multivariate rate ratio (RR) of pancreatic cancer for obese women and men (BMI ≥30 kg/m²) was 1.81 (95% CI: 1.04–3.15) compared to those with a BMI of 20–25 kg/m². For a difference of 20 cm (about two standard deviations) in waist circumference, the multivariate RRs were 1.32 (95% CI: 0.73–2.37) among women and 1.74 (95% CI: 1.00–3.01) among men. Pancreatic cancer risk was associated with history of diabetes (multivariate RR: 1.88; 95% CI: 1.09–3.26) and cigarette smoking (multivariate RR for current compared with never smokers: 3.06; 95% CI: 1.99–4.72). Current smokers of >40 pack-years had a five-fold elevated risk compared with never smokers. Risk among past smokers approached the RR for never smokers within 5–10 years following smoking cessation. Findings from this prospective study support positive relationships of overall obesity, abdominal adiposity, diabetes and smoking with risk of pancreatic cancer.

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Cancer of the pancreas, the sixth leading cause of cancer death in the European Union (Boyle and Ferlay, 2005), is a rapidly fatal malignancy. Less than 5% of patients survive 5 years after diagnosis (Sant et al, 2003). Primary prevention of pancreatic cancer is therefore of particular importance. Unfortunately, the etiology of pancreatic cancer remains largely elusive. Cigarette smoking is the only generally accepted modifiable risk factor, but explains only 25–29% of pancreatic cancer incidence (Silverman et al, 1994; Fuchs et al, 1996).

Evidence from in vitro, animal and human studies indicates that insulin, insulin resistance and abnormal glucose metabolism may play a role in pancreatic cancer etiology (Fisher et al, 1996; Gapstur et al, 2000; Schneider et al, 2001; Jee et al, 2005). Moreover, epidemiological studies have suggested a relationship between diabetes mellitus and increased risk of pancreatic cancer (Huxley et al, 2005). Obesity, and specifically abdominal adiposity, has been linked to metabolic abnormalities, including insulin resistance, hyperinsulinemia, glucose intolerance and to the development of diabetes mellitus (Kahn and Flier, 2000; IARC, 2002). Thus, obesity may be a risk factor for pancreatic cancer. However, epidemiological studies of body mass index (BMI), as a measure of overall obesity, in relation to risk of pancreatic cancer have yielded inconsistent results with a positive association observed in some, but not all studies (Berrington de Gonzalez et al, 2003). To our knowledge, no study has investigated the association between waist circumference, as an estimate of abdominal adiposity, and risk of pancreatic cancer.

In two prospective population-based cohorts of Swedish women and men, we examined the relationships between overall obesity (reflected by BMI) and abdominal adiposity (waist circumference) and the risk of pancreatic cancer. In addition, we report findings for diabetes, cigarette smoking and smoking cessation on pancreatic cancer risk.

MATERIALS AND METHODS

Study population

Two population-based prospective cohort studies provided data for the present analyses: the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM). The SMC was established between 1987 and 1990, when all women born between 1914 and 1948 and living in central Sweden (Västmanland and Uppsala counties) received a mailed questionnaire that elicited...
Cox proportional hazards models (Cox and Oakes, 1984) were used to estimate rate ratios (RRs) with 95% confidence intervals (CIs). Age (in months) and sex were controlled for as stratification variables in the Cox model. In multivariate models, we included education (less than high school, high-school graduate, or more than high school), BMI (< 20.0, 20.0 – 25.0, 25.0 – 29.9, or ≥ 30 kg/m²), physical activity (four categories), history of diabetes (yes or no), cigarette smoking (never, past < 20 pack-years, past ≥ 20 pack-years, current < 20 pack-years, current 20 – 39 pack-years, or current ≥ 40 pack-years) and alcohol consumption (quartiles). Multivariate analyses of waist circumference were further controlled for height (quartiles). Trends tests for BMI and waist circumference were performed by scoring the categories and entering the score as a continuous term in the model. Second-order interaction between BMI and cigarette smoking in relation to pancreatic cancer risk was tested using the likelihood ratio test. We used the SAS statistical package (version 9.1; SAS Institute, Inc., Cary, NC, USA) for all analyses. All statistical tests are two-sided.

RESULTS

A total of 136 incident cases (61 females and 75 males) of pancreatic cancer were diagnosed during 560 666 person-years of follow-up, yielding a crude incidence rate of 24.3 per 100 000 person-years. The incidence rate was similar among women (24.1 per 100 000 person-years) and men (24.4 per 100 000 person-years). The mean (± s.d.) age of the participants at baseline in 1997 was 62 (9.3) years for women and 60 (9.7) years for men. The median (± s.d.) age of the participants at time of diagnosis of pancreatic cancer was 72 (8.5) years for female cases and 72 (8.0) years for male cases. Table 1 presents the baseline characteristics by BMI. The mean (± s.d.) baseline BMI was 25.0 (3.9) kg/m² among women and 25.8 (3.4) kg/m² among men. In all, 34% percent of the women and 46% of the men were overweight (BMI 25 – 29.9 kg/m²); 11% percent of the women and 10% of the men were obese (BMI ≥ 30 kg/m²). Compared with women and men with a BMI of 20 – 25 kg/m², obese women and men were less likely to have a post-secondary education and to be current smokers, but were more likely to have diabetes; they also exercised less and had lower alcohol consumption. BMI was strongly correlated with waist circumference (women, r = 0.76; men, r = 0.75). The proportions of never, past and current smokers, respectively, at baseline were 54, 27 and 19% among women and 36, 46 and 18% among men.

We observed a positive association between BMI and risk of pancreatic cancer (Table 2). After controlling for age and other potential risk factors for pancreatic cancer, women and men with a BMI of 30 kg/m² or higher had an 81% increased risk compared with those with a BMI of 20 – 25 kg/m². When analysed as a continuous variable, an increment of 1 BMI unit (kg/m²) was related to a 4% increased risk of pancreatic cancer among women and men combined (RR: 1.05; 95% CI: 1.00 – 1.10), a 4% increased risk among women (RR: 1.04; 95% CI: 0.97 – 1.11), and a 6% increased risk among men (RR: 1.06; 95% CI: 0.99 – 1.14). The findings for BMI did not change appreciably after excluding cases that occurred within the first year of follow-up. Waist circumference was also positively associated with risk of pancreatic cancer, and similar to the observed association for BMI; the risk was greater among men (Table 2). For a difference of 20 cm (approximately two standard deviations) in waist circumference, the multivariate RRs were 1.32 (95% CI: 0.73 – 2.37) among women and 1.74 (95% CI: 1.00 – 3.01) among men.

A history of diabetes was associated with a statistically significant 1.9-fold elevated risk of pancreatic cancer (Table 2). This association remained after early follow-up cancers (i.e., those diagnosed within the first year) were excluded (RR: 1.97; 95%
The association with diabetes seemed to be confined to men, but the number of diabetic women with pancreatic cancer was small (n = 5).

Women and men who were current smokers at baseline had a significantly higher risk of pancreatic cancer compared with never smokers (Table 3). Past smoking was not related to a significantly increased risk, although women who had smoked in the past had a nonsignificant elevation in risk. Risk of pancreatic cancer increased with increasing number of pack-years of smoking. Current smokers of 40 or more pack-years had a fivefold elevated risk of pancreatic cancer compared to never smokers. An increment of 10 pack-years of smoking was associated with a multivariate RR of 1.36 (95% CI: 1.15–1.61; P value for trend = 0.0003).

We also assessed the association between smoking cessation and risk of pancreatic cancer (Figure 1). Compared with current smokers, the RR among past smokers diminished steeply and approached the RR for never smokers within 5–10 years following smoking cessation.

Figure 2 shows the RRs of pancreatic cancer according to cross-classification of BMI and smoking status. High BMI and cigarette smoking were independently associated with increased risk of
pancreatic cancer and there was no apparent effect modification between these variables (\(P\) for interaction = 0.74). Compared with nonsmokers (never and past) with a BMI of less than 25 kg/m\(^2\), current smokers with a BMI of 30 kg/m\(^2\) or more, had a multivariate RR of 5.07 (CI: 1.93 – 13.30).

**DISCUSSION**

In this prospective analysis, we observed approximately a doubling of the risk of pancreatic cancer for obese women and men (BMI \(\geq 30\) kg/m\(^2\)) compared with those with a normal weight (BMI 20 – 25 kg/m\(^2\)). We also confirmed associations between history of diabetes and cigarette smoking and increased risk of pancreatic cancer. In addition, we found that smokers who had quit smoking for 5 – 10 years had a risk of developing pancreatic cancer similar to that of never smokers. To our knowledge, this was the first study to evaluate the relationship between waist circumference (reflecting abdominal adiposity) and risk of pancreatic cancer. We found that waist circumference was positively associated with pancreatic cancer risk, particularly among men. A previous cohort study found that women and men who reported 'central' weight gain had increased relative risk of pancreatic cancer compared with women and men who reported peripheral weight gain; the association was stronger among men (Patel et al, 2005).

Previous studies of BMI and pancreatic cancer risk have produced inconsistent results. A recent meta-analysis of 14 studies...
on obesity and risk of pancreatic cancer estimated a 19% increase in risk among obese individuals compared with those with a normal weight (RR: 1.19; 95% CI: 1.10–1.29 for BMI 30 vs 22 kg/m2) (Berrington de Gonzalez et al., 2003). The summary risk estimate was higher when the authors excluded studies that did not control for smoking; the estimate was also higher for cohort than for case–control studies (Berrington de Gonzalez et al., 2003). Since that meta-analysis, two case–control studies based on direct patient interviews (Pan et al., 2004; Fryzek et al., 2005) and two cohort studies (Samanic et al., 2004; Patel et al., 2005) have reported a statistically significant positive relation between BMI and pancreatic cancer risk in both women and men or only in men. Another cohort of elderly women observed no increase in pancreatic cancer risk with greater BMI (Sinner et al., 2005).

In the present study, we observed a 1.9-fold higher risk of pancreatic cancer among women and men with diabetes. A meta-analysis of 17 case–control and 19 cohort or nested case–control studies (Huxley et al., 2005) showed a 1.8-fold higher risk of pancreatic cancer associated with a history of diabetes; the magnitude of the positive association was greater among individuals whose diabetes had been recently diagnosed.

A metabolic consequence of obesity, particularly the accumulation of intra-abdominal fat, is the development of insulin resistance, which leads to an increase in the secretion of insulin from the pancreas (IARC, 2002). A role of hyperinsulinemia in pancreatic pathogenesis might be through an increase in local blood flow and cell division in the pancreas (Henderson et al., 1981). The exocrine pancreatic cells are exposed to very high insulin concentrations through a portal circulation system from the insulin-producing pancreatic islets (Williams and Goldfine, 1985). High concentrations of insulin are able to activate the insulin-like growth factor I (IGF-I) receptor, and activation of this receptor leads to growth-promoting effects (Le Roith, 1997). Furthermore, excess insulin, through downregulation of the insulin-like growth factor binding protein-1, could result in an increase in the exposure to free IGF-I (Giovannucci, 2003). Both insulin and IGF-I have been shown to promote growth in pancreatic cell lines (Ohmura et al., 1990; Takeda and Escribano, 1991; Bergmann et al., 1995; Fisher et al., 1996).

This study has several strengths. The prospective design precluded recall bias and the need to use next-of-kin respondents. In addition, we had virtually complete follow-up as incident cases of pancreatic cancer were ascertained by record linkage to the Swedish Cancer Registry. Differential follow-up is therefore unlikely to have affected our results. We were also able to control for potential confounding by most known or possible risk factors for pancreatic cancer. Because data regarding exposures were collected before the diagnosis of pancreatic cancer, any misclassification would be nondifferential and would most likely have weakened rather than exaggerated any true associations. A limitation of this study is the self-reported information on anthropometric measures, diabetes and cigarette smoking. Overweight and obese individuals tend to underestimate their body size (weight, BMI, waist) to a greater extent than those who are lean, and shorter individuals tend to overestimate their height (Kuskowska-Wolk et al., 1989; Spencer et al., 2004). These biases are likely to attenuate risk estimates of the relations between BMI and waist circumference and risk of pancreatic cancer; thus the associations may be even stronger in the absence of measurement error. Another limitation of our study is the lack of information on timing of diagnosis of diabetes.

In summary, results from this population-based prospective study suggest that obesity may increase the risk for pancreatic cancer. Findings from this study also provide further support for associations of history of diabetes and cigarette smoking with pancreatic cancer risk.

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