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Lifestyle, dietary, and medical history factors associated with pancreatic cancer risk in Ontario, Canada

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Abstract
Objectives Pancreatic adenocarcinoma has one of the worst survival rates of all the cancers. Established risk factors for this malignancy are smoking, body mass index (BMI) and family history of pancreatic cancer. Findings are inconsistent regarding pancreatitis, diabetes, allergies, intake of fruit, vegetables, red meat, alcohol, caffeine, vitamin C, calcium, and folate supplements. Possible pancreatic cancer risk factors were evaluated within the population-based Ontario Pancreas Cancer Study.
Methods Pathologically confirmed pancreatic cancer cases ($n = 422$) were identified from the Ontario Cancer Registry between 2003 and 2007. Controls ($n = 312$) were recruited through random digit dialing. Data were collected using self-administered questionnaires. Multivariate logistic regression was used to obtain odds ratios.
Results Smoking, BMI, family history of pancreatic cancer, and caffeine were significantly associated with increased pancreatic cancer risk, while fruit intake and allergies significantly decreased risk. No other significant associations were observed in the multivariate model. Effect modification by smoking status was suggested for caffeine, family history of pancreatic cancer, BMI, and fruit.
Conclusions This study further clarifies the association between several lifestyle, dietary and medical history factors, and pancreatic cancer risk, many of which are potentially modifiable. Possible effect modification by smoking status should be further explored in future etiologic studies.

Keywords Pancreatic neoplasms · Risk factors · Diet · Smoking · Case–control studies

Abbreviations

AOR	Age-adjusted odds ratio
BMI	Body mass index
CI	Confidence interval
MVOR	Multivariate-adjusted odds ratio
OCR	Ontario Cancer Registry
OFCCR	Ontario Familial Colon Cancer Registry
OPCS	Ontario Pancreas Cancer Study
OR	Odds ratio

Introduction

It is estimated that 3,800 Canadians will be diagnosed with pancreatic adenocarcinoma in 2008 and 3,700 deaths are expected from this disease [1]. Although the incidence of pancreatic cancer is fairly low, pancreatic cancer is unique in that it has the worst survival rate of all the cancers in Canada; the estimated 5-year survival rate for pancreatic cancer is only 6% [1]. In addition to advanced age, cigarette smoking and family history of pancreatic cancer are the most well-established risk factors [2, 3]. There is also an increasing body of evidence that body mass index (BMI) or body fatness is positively associated with risk [2, 4–6]. History of chronic pancreatitis [7] and diabetes

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mellitus [5, 7–9] is associated with increased risk although there is speculation that these may be early signs of pancreatic cancer or share a common cause [2, 10]. There is limited, although fairly consistent, evidence that having allergies is associated with decreased pancreatic cancer risk [11–13].

The evidence on dietary intake and pancreatic cancer risk is less conclusive [2, 10]. The recent World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) review on diet and cancer found probable evidence that foods containing folate are associated with a decreased pancreas cancer risk, suggestive of evidence that fruits are associated with a decreased risk and red meat with an increased risk; while the evidence was inconclusive for vegetables, tea, alcohol, milk and dairy products, vitamin C and folic acid supplements, and coffee was not found to be associated with risk [6].

The objective of this study was to investigate the association between several suspected risk factors identified in earlier studies and pancreatic cancer risk in Ontario, Canada. A population-based case–control study design was used to evaluate the association between pancreatic cancer risk and BMI, smoking, family history of pancreatic cancer, chronic pancreatitis, diabetes mellitus, allergies, alcoholic and caffeinated beverages, fruit, vegetable, and red meat intake, and calcium, folate and vitamin C supplementation.

Materials and methods

Study design

The Ontario Pancreas Cancer study (OPCS) is a population-based case–control study that commenced on 1 April 2003 with continuing enrollment. The OPCS is one of seven study sites which contribute data on genetic and epidemiologic factors among pancreatic cancer cases to the multidisciplinary Pancreatic Cancer Genetic Epidemiology (PACGENE) Consortium [14]. Ethics approval was obtained from Mount Sinai Hospital and University Health Network Research Ethics Boards prior to commencing data collection. More details on the OPCS are provided below and also published elsewhere [11].

Cases

Cases were identified between April 2003 and December 2007 through the Ontario Cancer Registry, which employs a rapid-case ascertainment system (electronic pathology reports submitted within several weeks). Men and women living in Ontario with a first primary, pathologically confirmed adenocarcinoma of the pancreas or adenocarcinoma metastasis, confirmed as pancreatic cancer by treating physicians, were considered eligible for the OPCS (International Classification of Diseases for Oncology Third Edition codes C25.0–25.9). Eligible cases were mailed a study package after the physicians' consent was obtained. The study package consisted of three questionnaires, a Personal History (epidemiology) Questionnaire, a Clinical Patient Questionnaire and a Family History Questionnaire. After completion of the questionnaires the participants were also asked to provide blood (DNA) samples. Cases over age 80 were excluded from this study analysis.

Controls

Controls were a random sample of Ontario residents identified using the Ministry of Finance property assessment rolls and also random digit dialing. Controls had initially been recruited to participate as controls in the Ontario Familial Colon Cancer Registry (OFCCR) [15]. Eligible controls included men and women <75 years of age, residing in the Greater Toronto Area, with no personal history of pancreas or colorectal cancer. The OPCS contacted controls by mail, during 2002–2003, and participants were mailed a Personal History (epidemiology) Questionnaire.

Data collection

Mailed self-administered Personal History Questionnaires asked for information on subject characteristics, medical history, and selected lifestyle and dietary factors, in addition to other items. All variables were defined with respect to at least one year prior to completing the questionnaire. Dietary factors were measured by frequency of consumption (daily, weekly or yearly) for a stated portion size. For example, for fruit consumption participants were asked: "About one year ago, how often did you eat a piece or serving of fruit? (One serving of fruit is: 1 medium-sized fresh fruit; ½ cup of chopped, cooked or canned fruit; ¼ cup of dried fruit; 6 ounces of fruit juice.)". Well-established and possible pancreatic cancer risk factors identified from the literature were investigated in this analysis. Previous results have been published from the OPCS reporting an inverse association between pancreatic cancer risk and allergies; the same allergy variable was included in this study of all risk factors [11].

Statistical analysis

All analyses were conducted using SAS 9.1 [16]. Variables were categorized on the basis of pre-established cut points (e.g., BMI) or based roughly on tertiles among controls. Age was calculated at pancreas cancer diagnosis date for

cases and age at referent date of 1 January 2003 (midpoint of case recruitment) for controls. Age-adjusted odds ratios (AORs), multivariate odds ratios (MVORs), and 95% confidence intervals (CI) were obtained using unconditional logistic regression. AORs (adjusted only for age) were examined for each risk factor. Subsequently, a full predictive multivariate model was constructed that included all of the suspected risk factors and subject characteristics (age, sex, and education). Working backward from the full model variables were manually removed to create the most parsimonious final model. Variables were excluded from the final model only if they had *p*-values for the Wald chi-square test >0.20 (i.e., they were not significantly associated with pancreas cancer risk) and if removal did not substantially change the MVORs for the remaining variables in the model (i.e., they did not confound other associations). The final multivariate model contained the same variables as a model constructed using an automated selection procedure in SAS (either backward elimination or stepwise selection with *p*-values set at 0.20 to leave and 0.15 to enter the model). Statistical significance of the interactions between each variable and sex and smoking were tested using the Likelihood Ratio test. Statistical significance was defined as p-value < 0.05 and all tests were two-sided.

Results

Overall, 1,740 cases of pancreatic cancer were identified between April 2003 and December 2007. Of these, 559 (32%) were deceased at contact, 488 (28%) refused or physician consent was not obtained, 234 (13%) we were unable to contact, and 37 (2%) had not returned the questionnaire (non-responders) or were over the age of 80 (ineligible). Data for this study were available from 422 eligible cases (45% of contacted living cases). Among the controls, 312 out of 378 (83%) mailed the OPCS Personal History Questionnaire returned the completed questionnaires. The mean age (years) of the cases and controls was 63 (standard deviation [SD] = 9.9) and 66 (SD = 7.9), respectively. Slightly more men (56%) than women (44%) completed the study. Cases were less well educated than controls with 48% of cases versus 35% of controls having no postsecondary education. Proxy respondents were used for 47 (11%) of cases. Removal of the 47 proxy respondents from the dataset did not change the final models (results not shown).

Table 1 provides the frequencies by case and control status and the AORs for all subject characteristics and the suspected medical history and lifestyle pancreatic cancer risk factors. Table 2 provides the same information for the dietary factors. The MVOR estimates for the final parsimonious model (including: age, education, BMI, smoking status, family history of pancreatic cancer, weekly fruit servings, caffeinated beverages, alcohol, and allergies) are also provided in Tables 1 and 2. Note: The MVORs for this final model were essentially unchanged from those in a multivariate model with all the 17 variables. The Hosmer and Lemeshow Goodness of Fit test results showed no evidence of lack of fit. No statistically significant interactions with sex were found (results not shown) and the ORs for all the variables were of similar magnitude when the analyses were repeated stratified by sex (i.e., no effect modification); thus, males and females are combined for all analyses.

The age-adjusted and multivariate analyses (Table 1) showed that, as expected, smoking, BMI, and family history of pancreatic cancer were associated with increased risk of pancreatic cancer. Among current smokers there was a tripling of pancreatic cancer risk (MVOR = 3.24, 95% CI: 1.49–7.05); however, no increased risk was observed among former smokers (MVOR = 0.96, 95% CI: 0.65–1.41). BMI $\geq$ 30 (obese) was strongly associated with increased risk of pancreas cancer (MVOR = 3.51, 95% CI: 1.92–6.39). Among overweight persons (BMI: 25–29.9) the risk was still nearly twice that of those with a normal BMI (<25). A family history of pancreatic cancer was associated with a significant fourfold increased risk (MVOR = 4.16, 95% CI: 1.68–10.30).

Several "suspected" risk factors were also evaluated. Chronic pancreatitis was found to be associated with increased risk in the age-adjusted model, yet after adjustment for other variables this association approached null and was not significant. No significant association was found between diabetes and pancreatic cancer risk. As previously reported in this study [11], allergies were significantly associated with reduced risk of pancreatic cancer, and this reduced risk remained even after adjustment for other variables (MVOR = 0.40, 95% CI: 0.26–0.59).

Among the foods investigated (Table 2), fruit intake was found to be significantly associated with decreased risk of pancreatic cancer in a dose-response manner, such that those who consumed greater than 14 servings of fruit per week (vs. <7) had a 50% decrease in risk. No significant associations were observed between vegetable or meat intake and pancreatic cancer risk. A trend toward increased risk with red meat consumption was observed although the confidence intervals were quite wide. In addition, the associations with red meat were attenuated in the multivariate analyses and did not confound the risk estimates for other variables, and thus red meat was not included in the final multivariate model. Additional analysis by meat appearance after cooking (e.g., how well-done meat was cooked) did not reveal any significant associations (results not shown here).

Table 1 Distribution of pancreatic cancer cases, controls, age-adjusted odds ratio (AOR) for subject characteristics and suspected medical history and lifestyle pancreatic cancer risk factors and multivariate-adjusted odds ratios (MVORs) for variables significantly associated with pancreatic cancer risk

Variable	Cases ($n = 422$) No. (%)[a]	Controls ($n = 312$) No. (%)[a]	AOR[b] (95% CI)	MVOR[c] (95% CI)
Subject Characteristics				
Age (years)				
≤49	33 (8)	11 (4)	N/A	N/A
50–54	58 (14)	19 (6)		
55–59	63 (15)	29 (9)		
60–64	67 (16)	58 (19)		
65–69	85 (20)	71 (23)		
70–74	58 (14)	78 (25)		
75–79	58 (14)	45 (15)		
Sex				
Male	233 (55)	176 (56)	1.00 (referent)	Not included[d]
Female	189 (45)	136 (44)	1.08 (0.80–1.47)	
Education				
High school or less	202 (48)	106 (35)	1.00 (referent)	1.00 (referent)
Some college/ university	73 (17)	92 (30)	0.37 (0.25–0.56)	0.56 (0.35–0.89)
College/university grad	143 (34)	109 (35)	0.55 (0.38–0.79)	0.93 (0.60–1.44)
Medical history				
Chronic pancreatitis[e]				
No	398 (95)	305 (99)	1.00 (referent)	Not included[d]
Yes	21 (5)	4 (1)	3.50 (1.17–10.46)	
Diabetes mellitus[f]				
No	371 (88)	274 (89)	1.00 (referent)	Not included[d]
Yes	50 (12)	34 (11)	1.21 (0.75–1.94)	
Family history of pancreatic cancer[g]				
No	379 (90)	304 (97)	1.00 (referent)	1.00 (referent)
Yes	43 (10)	8 (3)	3.80 (1.74–8.30)	4.16 (1.68–10.30)
Allergies[h]				
No	328 (79)	202 (65)	1.00 (referent)	1.00 (referent)
Yes	86 (21)	107 (35)	0.44 (0.31–0.62)	0.40 (0.26–0.59)
Lifestyle factors				
BMI (kg/m^2)[i]				
<25	148 (36)	143 (51)	1.00 (referent)	1.00 (referent)
25–29.9	183 (44)	110 (39)	1.78 (1.26–2.50)	1.77 (1.19–2.62)
≥30	83 (20)	26 (10)	3.18 (1.91–5.31)	3.51 (1.92–6.39)
Smoking status				
Never	162 (40)	143 (46)	1.00 (referent)	1.00 (referent)
Former	187 (46)	152 (49)	1.06 (0.77–1.46)	0.96 (0.65–1.41)
Current	60 (15)	14 (5)	3.62 (1.92–6.83)	3.24 (1.49–7.05)

[a] Numbers may not add to total due to missing values

[b] *AOR*, Age-adjusted odds ratio. Age at pancreas cancer diagnosis date for cases and at referent date of 1 January 2003 (midpoint of case recruitment) for controls

[c] *MVOR*, Multivariate-adjusted odds ratios. Parsimonious model adjusted for all variables significant in the multivariate model (age, education, BMI, smoking status, family history of pancreatic cancer, weekly fruit servings, alcohol, caffeinated beverages, and allergies)

[d] Variables excluded from the multivariate model as they were not significantly associated with pancreatic cancer after adjustment for other variables and did not confound the association of any variables in the model

[e] Diagnosed with chronic pancreatitis prior to 1 year ago

[f] Diagnosed with diabetes mellitus prior to 2 years ago

[g] History of pancreatic cancer in first or second degree relative

[h] Ever had allergies or hay fever prior to 1 year ago

[i] Body Mass Index (BMI) calculated as usual adult weight (kg) divided by height (m) squared

Caffeinated beverage consumption was associated with increased cancer risk. Among those who drank ≥3 caffeinated beverages per day (vs. <1 per day) the risk doubled (MVOR = 2.29, 95% CI: 1.29, 4.08). Further analysis by type of caffeinated beverage (coffee, tea, or soft drink) revealed that this association was mostly driven by coffee consumption (≥3 per day vs. <1 per day MVOR = 2.05, 95% CI: 1.15, 3.66); there were no significant associations between either caffeinated tea (≥1 per day vs. <1 per month MVOR = 1.45, 95% CI: 0.93, 2.26) or caffeinated soft drinks (≥1 per day vs. <1 per month MVOR = 1.24, 95% CI: 0.66, 2.33). Contrary to our expectations, statistically significant inverse associations were observed between alcohol consumption and pancreatic cancer risk

Table 2 Distribution of pancreatic cancer cases, controls, age-adjusted odds ratio (AOR) for suspected dietary pancreatic cancer risk factors and multivariate-adjusted odds ratios (MVOR) for variables significantly associated with pancreatic cancer risk

Variable	Cases ($n = 422$) No. (%)[a]	Controls ($n = 312$) No. (%)[a]	AOR[b] (95% CI)	MVOR[c] (95% CI)
Alcohol[d]				
<1 per week	207 (49)	119 (39)	1.00 (referent)	1.00 (referent)
1–6 per week	94 (22)	104 (34)	0.47 (0.32–0.68)	0.50 (0.32–0.78)
≥1 per day	118 (28)	82 (27)	0.86 (0.59–1.24)	0.88 (0.56–1.38)
Caffeinated beverages[e]				
<1 per day	55 (13)	67 (22)	1.00 (referent)	1.00 (referent)
1–2 per day	241 (57)	171 (56)	1.92 (1.24–2.92)	2.37 (1.41–3.97)
≥3 per day	125 (30)	70 (23)	2.26 (1.41–3.63)	2.29 (1.29–4.08)
Weekly fruit servings				
≤7	237 (59)	135 (46)	1.00 (referent)	1.00 (referent)
8–14	103 (26)	98 (33)	0.58 (0.41–0.83)	0.59 (0.38–0.90)
>14	64 (16)	63 (21)	0.55 (0.36–0.83)	0.54 (0.34–0.87)
Calcium supplement[f]				
No	300 (73)	189 (62)	1.00 (referent)	Not included[g]
Yes	108 (26)	116 (38)	0.67 (0.48–0.93)	
Vitamin C supplement[f]				
No	309 (75)	206 (68)	1.00 (referent)	Not included[g]
Yes	97 (24)	97 (32)	0.71 (0.51–1.00)	
Folate supplement[f]				
No	376 (94)	274 (93)	1.00 (referent)	Not included[g]
Yes	20 (5)	20 (7)	0.84 (0.43–1.64)	
Weekly vegetable servings				
≤7	201 (49)	142 (47)	1.00 (referent)	Not included[g]
8–21	177 (43)	132 (44)	0.94 (0.69–1.30)	
>21	29 (7)	29 (10)	0.66 (0.39–1.24)	
Weekly red meat servings				
≤1	99 (26)	83 (32)	1.00 (referent)	Not included[g]
2–3	151 (40)	107 (41)	1.16 (0.78–1.72)	
>3	131 (34)	73 (28)	1.49 (0.98–2.28)	

[a] Numbers may not add to total due to missing values

[b] *AOR*, Age-adjusted odds ratio. Age at pancreas cancer diagnosis date for cases and at referent date of 1 January 2003 (midpoint of case recruitment) for controls

[c] *MVOR*, Multivariate-adjusted odds ratios. Parsimonious model adjusted for all variables significant in the multivariate model (age, education, BMI, smoking status, family history of pancreatic cancer, weekly fruit servings, alcohol, caffeinated beverages, and allergies)

[d] Average number of alcoholic beverages (beer, wine and liquor) consumed prior to 1 year ago

[e] Average number of caffeinated beverages (caffeinated coffee, tea and soft drinks) consumed prior to 1 year ago

[f] Taken supplement regularly (at least once per week for at least 1 year) prior to 1 year ago

[g] Variables excluded from the multivariate model as they were not significant variables of pancreatic cancer after adjustment for other variables and did not confound the association of any variables in the model

(Table 2). This inverse association remained in the adjusted analyses and was statistically significant for those who drank 1–6 alcoholic drinks per week, but not among those who drank more than one drink per day.

The use of calcium supplements was significantly associated with reduced risk of pancreatic cancer in the age-adjusted analysis (AOR = 0.67, 95% CI: 0.48, 0.93), yet after adjustment for other variables this association no longer remained significant, and thus calcium was not included in the final multivariate model. Similarly, there was a borderline significant inverse association observed between vitamin C and pancreatic cancer risk in the age-adjusted analyses (AOR = 0.71, 95% CI: 0.51–1.00), but this did not persist after adjustment for other variables. The use of folate supplements was not significantly associated with pancreatic cancer risk.

Table 3 Multivariate-adjusted odds ratios (MVORs) for variables significantly associated with pancreatic cancer risk stratified by smoking status

Variable	Never smoker $n = 321$ MVOR[a] (95% CI)	Ever smoker n = 429 MVOR[a] (95% CI)	p-value for interaction[b]
Caffeinated beverages[c]			
<1 per day	1.00 (referent)	1.00 (referent)	0.04
1–2 per day	1.47 (0.71–3.08)	4.07 (1.88–8.81)	
≥3 per day	0.94 (0.38–2.31)	5.20 (2.26–11.98)	
Family history of pancreatic cancer[d]			
No	1.00 (referent)	1.00 (referent)	0.06
Yes	12.63 (2.58–61.95)	2.01 (0.61–6.64)	
BMI (kg/m^2)[e]			
<25	1.00 (referent)	1.00 (referent)	0.09
25–29.9	2.45 (1.34–4.50)	1.23 (0.71–2.15)	
≥30	6.86 (2.67–17.78)	1.84 (0.83–4.08)	
Weekly fruit servings			
≤7	1.00 (referent)	1.00 (referent)	0.23
8–14	0.85 (0.45–1.61)	0.44 (0.25–0.80)	
>14	0.82 (0.39–1.66)	0.35 (0.18–0.69)	
Alcohol[f]			
<1 per week	1.00 (referent)	1.00 (referent)	0.39
1–6 per week	0.61 (0.31–1.21)	0.44 (0.24–0.83)	
≥1 per day	0.86 (0.45–1.61)	1.02 (0.55–1.89)	
Allergies[g]			
No	1.00 (referent)	1.00 (referent)	0.63
Yes	0.45 (0.24–0.82)	0.32 (0.18–0.57)	

[a] *MVOR*s, Multivariate-adjusted odds ratios. Adjusted for age, education, and all variables in the table

[b] Likelihood ratio test for interaction

[c] Average number of caffeinated beverages (caffeinated coffee, tea and soft drinks) consumed prior to 1 year ago

[d] History of pancreatic cancer in first or second degree relative

[e] Body Mass Index (BMI) calculated as usual adult weight (kg) divided by height (m) squared

[f] Average number of alcoholic beverages (beer, wine and liquor) consumed prior to 1 year ago

[g] Ever had allergies or hay fever prior to 1 year ago

Table 3 presents the results of the multivariate analysis stratified by smoking status—never smoker versus ever smoker (current and former). A statistically significant interaction was observed between smoking and caffeinated beverage consumption ($p = 0.04$). Among ever smokers, caffeinated beverage consumption was associated with cancer risk, whereas no association was observed among never smokers. Interactions between smoking status and other variables were not of statistical significance (Table 3); however, the magnitude of association for family history of pancreatic cancer, BMI, and fruit was appreciably modified by smoking status. Family history of pancreatic cancer and BMI were both significantly associated with increased risk of pancreatic cancer among never smokers, but not among ever smokers. In contrast, the inverse association between fruit consumption and pancreatic cancer risk was only significant among ever smokers.

Discussion

The findings of this study suggest that smoking, BMI, family history of pancreatic cancer, and caffeine intake are all risk factors for adenocarcinoma of the pancreas while fruit intake and allergy history are associated with a decreased risk of pancreas cancer. Consistent with previous studies, we found an increased risk of pancreas cancer among current smokers while no association with former smokers was observed [17, 18]. Furthermore, smoking status appeared to modify the association between several risk factors and pancreatic cancer risk. Both BMI and family history of pancreatic cancer were found to be positively associated with pancreatic cancer risk overall and even stronger so among never smokers, but among ever smokers these risk factors were no longer significant. In accordance with previous reviews, we found that BMI is

associated with increased pancreatic cancer risk [4–6]. Results from a meta-analysis of 21 prospective studies reported a pooled OR of 1.12 (95% CI: 1.06–1.17) for a 5 kg/m^2 increase in BMI [4]. Inconsistent with most of the literature (including this study), a previous Canadian study of BMI and pancreatic cancer risk found a positive association only among men and not women [19]. However, the previous study categorized BMI differently and did not adjust for the same variables as in this study. We observed no significant differences between men and women in regard to the association between BMI and pancreatic cancer risk. Our finding regarding increased risk of pancreas cancer among individuals with a family history of pancreatic cancer is in agreement with the results of a meta-analysis of seven case–control studies (RR = 2.82, 95% CI: 1.99–3.66); however, our estimates overall and among current smokers were much stronger [20].

Diabetes mellitus and chronic pancreatitis have been associated with increased risk of pancreatic cancer, although, as reviewed elsewhere [2, 5, 7, 10, 21], the mechanism is not clear; it has been suggested that both pancreatitis and diabetes may be co-morbid conditions with pancreatic cancer or a common cause is shared. It is possible that diabetes mellitus and chronic pancreatitis are true risk factors for disease, but this study does not support that hypothesis as neither was significantly associated with cancer risk after adjustment for other variables. The null associations between diabetes and chronic pancreatitis were not modified by smoking status (data not shown). However, it is important to note that chronic pancreatitis was very rare in our dataset. As has been shown previously [11–13], allergies are associated with decreased risk of pancreatic cancer.

There is little consensus regarding the role of food and nutrition and pancreatic cancer risk [2, 6, 7, 10]. Our finding of no association between vegetable intake and pancreatic cancer risk is supported by some recent studies of overall vegetable intake [22, 23] although other studies have found an inverse association overall [24] or for specific subgroups of vegetables [23, 24]. We found that fruit intake was associated with decreased pancreatic cancer risk among our entire study population, and this is supported by some [22, 24], but not all [23], previous studies and reviews [6]. One potential reason for the inconsistent literature may be un-examined effect modification. After stratification by smoking status, the inverse association between fruit and pancreatic cancer risk existed only among ever smokers. Further work is needed to clarify specific fruits, and perhaps vegetables and their dietary components that are associated with pancreatic cancer risk and to further explore interactions with smoking and other variables. Recent reviews have concluded that the evidence on red meat and pancreatic cancer risk is inconclusive, although suggestive of an increased risk, and we propose that more research is needed regarding cooking method [2, 6]. We did not find that red meat intake was associated with pancreatic cancer risk, even after taking into consideration cooking time. No significant associations were observed for vitamin C, folate or calcium supplementation once adjustment was made for other variables. As reviewed elsewhere, the association between pancreatic cancer and vitamin C supplements is generally inverse [7, 25] or considered to be inconclusive [6]. Foods containing folate are inversely associated with pancreatic cancer risk, but there is no evidence for an effect of folate supplements [6, 26]. The research on foods containing calcium is inconclusive [6] and calcium supplements have not previously been studied on their own.

Multiple reviews have concluded that the body of literature does not support an association between pancreas cancer and either alcohol intake [2, 6, 7, 10, 25] or caffeinated beverage intake [2, 6, 7, 10, 25, 27]. In contrast, we observed a significant positive association between overall caffeinated beverage consumption and pancreatic cancer risk. Among the previous studies of caffeinated beverages [28–31], only one [31], which found no association, included a measure of total caffeine. The measurement of coffee alone has been found to underestimate total caffeine consumption and such misclassification may result in null findings [32]. It is possible that the associations observed between pancreatic cancer risk and risk factors such as caffeinated beverages may be due to residual confounding by smoking. If smoking status is not captured adequately (i.e., measurement error), then it is possible that residual confounding resulted in biased risk estimates and is responsible for the observed associations. Irrespective of caffeine, there are other unique components of coffee, tea, and soft drinks that may also be associated with cancer risk. There is some suggestion that sugared soft drinks might increase risk [33, 34]. Our measure of soft drinks included only those that were caffeinated and most study participants drank <1 per month (51% of cases and 55% of controls). In the multivariate analyses when coffee, tea, and soft drinks were each considered, instead of the combined caffeinated beverage variable, there was no statistically significant increased risk observed for soft drinks or tea.

In regard to alcohol intake, most studies have reported positive [28, 35–38] or null associations [31, 39, 40] although consistent with our results a few previous studies have reported some inverse (although not significant) associations with certain types and quantities of alcohol [29, 30, 38]. Few participants in this study consumed more than one alcoholic beverage per day, thus limiting our ability to draw any conclusions about high alcohol consumption. The interaction between alcohol and smoking was not statistically significant, as was also reported in a previous case–control study [40].

This is one of the few studies of pancreatic cancer risk factors to evaluate effect modification by smoking. A significant interaction and effect modification were observed for caffeine, with an increased risk observed only among smokers. The association between pancreatic cancer risk and family history of pancreatic cancer varied by smoking status, with the magnitude of association being 10-fold among never smokers while only a doubling of risk was observed for family history among ever smokers. In addition, there was some suggestion that BMI increases risk only among never smokers and fruit decreases risk only among ever smokers; however, these interactions were not statistically significant. This suggests that smoking might not only be important directly in relation to the etiology of pancreatic cancer, but also an effect modifier of other suspected risk factors. Many studies of pancreatic cancer, including ours, are limited by small sample size, thus limiting the ability to evaluate effect modification. To our knowledge, only one previous study has evaluated effect modification of many pancreas cancer risk factors by smoking status [41]. Among women, significant synergistic interactions were reported between smoking and both family history of pancreatic cancer and diabetes. No evidence of effect modification by smoking was reported in men. In this study, we only evaluated effect modification by smoking in men and women combined as there was no power to stratify our dataset on two variables. It is important that future studies of pancreatic cancer further investigate the interaction between smoking and risk factors and this will require much larger sample sizes.

There are some potential limitations of this study. Pancreatic cancer is not common and has a poor prognosis; thus our study sample size is relatively small and may lack statistical power for the less prevalent risk factors investigated and to investigate effect modification. In addition, a low response rate was obtained among cases and therefore possible response bias is a limitation of this study. The population-based Ontario Cancer Registry allowed for the identification of all pancreatic cancer cases. Comparing our pancreas cancer case response rates to previous population-based pancreatic cancer case–control studies is difficult as the calculation and reporting of response rates varies between studies. Among other Canadian studies that have identified cases from cancer registries the response rate has also been low. Studies conducted within the Canadian National Enhanced Cancer Surveillance System [19, 30, 42–44] reported a response rate of approximately 55% among eligible cases, but when cases who died prior to contact were included in the denominator the response rate is less than 30% [19]. Similarly another Canadian population-based case–control study reported a response rate of 60% among eligible cases, but of all identified cases the rate is approximately 40% [29, 45, 46].

It is probable that patients with a more advanced stage of cancer did not participate in this study as discussed elsewhere [11] and it is unknown how this survival bias might influence study results. During our study period, a rapid-case ascertainment system (electronic pathology reports submitted within several weeks) was employed by the Ontario Cancer Registry and this is especially helpful for the study of fatal cancers where rapid recruitment is essential. It is important for future studies to improve upon the poor response rates characteristic of pancreatic cancer studies. Every effort was made to follow-up with eligible cases. A follow-up postcard was sent within 2 weeks of the questionnaire mailing and a telephone call was made to non-respondents 2 weeks later. Messages were left for non-respondents and a new questionnaire package was mailed out when necessary.

As with all case–control studies, there is the potential for recall bias, although for most variables measured in this study, there is no reason to expect that cases and controls would respond differently. Furthermore, with the use of a questionnaire to measure risk factors there is the potential for measurement error and misclassification bias. However, it is expected that any misclassification would be non-differential which generally tends to bias toward the null [47]. A full food frequency questionnaire was not administered, limiting the number of foods, beverages, and supplements measured. Thus, total energy intake was not measured in this study. In regard to smoking, we found that the risk of pancreatic cancer among former smokers was not significantly different from that of never smokers. Length of time since quitting smoking is a potentially important factor that was not measured in this study. Future studies would benefit from more comprehensive measures of diet and smoking, including passive smoking, since this is an important component of cigarette smoke exposure. Finally, future studies should be designed with sufficient power to further explore the interactions between smoking history and pancreatic cancer risk factors.

One of the strengths of this study is that we were able to control for many variables simultaneously. Overall, the observed risk estimates are in the expected direction and magnitude of association for all the variables (except alcohol) and are consistent with previous literature. This study adds further support to the associations observed between dietary and lifestyle factors and pancreatic cancer risk, and suggests that interactions might exist between some risk factors and smoking status; however, larger studies are needed to explore this further. Some of the identified variables are modifiable and thus may be important in the prevention of this fatal malignancy. There is no screening test available for pancreatic cancer, thus identifying people at high risk (e.g., individuals with a family history of pancreatic cancer or obese persons) may

be an important first step in the primary prevention of pancreatic cancer.

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