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Risk Factors for Early-Onset and Very-Early-Onset Pancreatic Adenocarcinoma: A Pancreatic Cancer Case-Control Consortium (PanC4) Analysis

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Abstract

Objectives—While pancreatic cancer (PC) most often affects older adults, to date, there has been no comprehensive assessment of risk factors among PC patients under age 60.

Methods—We defined early onset PC (EOPC) and very early onset PC (VEOPC) as diagnosis of PC under ages 60 and 45, respectively. We pooled data from eight case-control studies, including 1,954 patients with EOPC and 3,278 age- and sex-matched controls. Logistic regression analysis was performed to identify associations with EOPC and VEOPC.

Results—Family history of PC, diabetes mellitus, smoking, obesity, and pancreatitis were associated with EOPC. Alcohol use ≥26 g daily also was associated with increased risk for EOPC (OR 1.49, 95% CI 1.21-1.84), and there appeared to be a dose- and age-dependent effect of alcohol on risk. The point estimate for risk for VEOPC was OR 2.18, (95% CI 1.17-4.09).

Conclusion—The established risk factors for PC, including smoking, diabetes, family history of PC, and obesity also apply to EOPC. Alcohol intake appeared to have an age-dependent effect; the strongest association was with VEOPC.

Keywords

Pancreatic Cancer; Alcohol; Early Onset; Very Early Onset; Smoking; Obesity

Introduction

In more developed regions of the world, pancreatic cancer is now the fifth commonest cause of cancer death (fifth in men and 4th in women).^{1, 2} Unless there are rapid improvements in treatment, it is predicted that pancreatic cancer will rank even higher in the future because mortality rates from breast cancer and colon cancer are continuing to decline, while pancreatic cancer incidence rates have been increasing and survival remains poor, with five-year survival rates under 5%.³

In the United States, the median age at diagnosis of pancreatic cancer is 71 years.⁴ Only about 20% of pancreatic cancers develop before age 60, with less than 3% prior to age 45.⁵ Nevertheless, early-onset pancreatic cancer (EOPC) contributes significantly to the total burden of pancreatic cancer because of greater number of years of potential life lost. Even

more devastating in this regard is very early-onset pancreatic cancer (VEOPC), diagnosed before age 45.

While hereditary factors are thought to play a greater role in early onset cancers,⁶ they do not explain most EOPC, and non-genetic risk factors contribute to the genesis of pancreatic cancer in all age groups. For both sporadic and familial pancreatic cancer, in addition to smoking, various other life style and environmental exposures, such as alcohol and tobacco are reported to influence age at diagnosis of this disease.⁷⁻⁹ However, a comprehensive analysis of risk factors specific to the youngest age groups for pancreatic cancer in a study large enough to distinguish risk factors for both EOPC and VEOPC has not been performed.

The Pancreatic Cancer Case-Control Consortium (PanC4) (<http://www.panc4.org>), is an international group of researchers organized to pool data from individual case-control studies of pancreatic cancer.¹⁰⁻¹³ We pooled data from participating PanC4 centers to examine age-specific risk factors for pancreatic cancer in patients diagnosed with young onset pancreatic cancer, previously described as patients under age 60 at diagnosis¹⁴. We performed further analyses by five-year increments to explore whether risk factors vary according to age.

Subjects and Methods

Eight independent case-control studies in the PanC4 contributed data to this analysis. Eligible pancreatic cancer cases were patients aged less than 60 years who had histologically confirmed pancreatic adenocarcinoma or a clinical diagnosis of pancreatic cancer. Patients known to have neuroendocrine or acinar tumors were excluded. Within each study, population- or hospital-representative controls were matched to the cases by age and sex. The final sample for analysis consisted of 1,954 cases (90% confirmed as adenocarcinoma by pathology) and 3,278 controls. The studies and sample descriptions are shown in Table 1.

Participating studies include Mayo Clinic (PI: Gloria Petersen, Clinic-based registry 2000-11)¹⁵, LSU (PI: Elizabeth Fontham, Cancer Registry 2001-6), MD Anderson (PI: Donghui Li, Cancer Registry)¹⁶, Yale (PI: Harvey Risch, Population-based 2005-09)¹⁷, UCSF (PI: Paige Bracci, Population-based 1995-99), SEARCH (International multicentric: PI: Peter A. Baghurst, Adelaide, Australia; PI: Antony B. Miller, Toronto, Canada; PI: H. Bas Bueno de Mesquita, Utrecht, The Netherlands; Parviz Ghadirian, Montreal, Canada; Witold Zatonski, Warsaw, Poland)¹⁸, Italy (PI: Talamini)¹⁹, Ontario (PI: Steven Gallinger, Cancer Registry 2003-7)²⁰.

Statistical Methods

A pooled analysis using case and control data from the eight PanC4 studies was used to evaluate the association between EOPC, VEOPC, and risk factors. Potential risk factors considered were identified from data available from the majority of studies. These factors were specified *a priori* and include: sex, personal history of diabetes or pancreatitis (both 3 years prior to diagnosis or study recruitment), family history of pancreatic cancer, cigarette smoking, alcohol consumption and typical adult body mass index (BMI, weight/height² kg/m²). To allow for differences in reporting across participating study sites and to minimize

numbers of participants excluded because of missing data, we included ‘unknown’ levels for covariates in our models. Smoking information was considered as: 1) ever/never; 2) current/former (<1 year since use)/never; 3) cumulative lifetime pack-years as both a continuous variable and in the following categories: never, 1 to <20, 20 to <40, 40; and 4) cigarettes per day as a continuous variable and in categories of never, <20, 20. Alcohol consumption was considered as: 1) ever regular consumption vs. never; and 2) grams of alcohol consumption per day as both a continuous variable and as <26 g vs. 26 g ethanol (2 drinks) per day. BMI was used as a continuous variable and as two categorical variables: 1) dichotomized at 30 kg/cm²; and 2) categorized as follows: <18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40, 40+ kg/cm². Once alcohol use was identified as a key finding of interest, dose-association analysis was performed for men and women to identify a potential threshold for increased risk.

A univariable logistic regression model was initially used to calculate odds ratios (ORs) and 95% confidence intervals for each of the potential risk factors. Due to inter-center variability in univariable risk estimates we adjusted all estimates for study center. We included a three-level site variable (non-US {Italy, Ontario, and SEARCH}, US: non-Mayo {Yale, LSU, MD Anderson}, US: Mayo) as a covariate in the final model.

Multivariable adjusted logistic regression models were then fit considering the potential risk factors including various quantifications of smoking. We evaluated smoking status, (current/former/never smoker), pack-years, smoking intensity (packs per day), in various models. All models were similar in effect of tobacco use on risk (data not shown). Pack years was chosen as the representative variable in the final model, as it best accounted for intensity and duration of exposure. Variables included in the final model were risk factors that were statistically associated with PC risk overall, along with the study site variable. Odds ratios (ORs) and 95% confidence intervals are presented in Table 2.

Additionally, stratified analyses that categorized age at diagnosis/interview by 5-year increments (<45, 45 to 49, 50 to 54, and 55 to 59) were used to investigate the risk of pancreatic cancer in different age groups. Models that fit interactions with age as a continuous variable for each factor were considered in order to address trends across age groups. All statistical analyses were performed using SAS/STAT software, version 9.2 of the SAS System for UNIX.

Results

Characteristics of cases and controls are shown in Table 1. Overall, 58% of cases and 61% of controls were male. Median age was 52 years (25th and 75th percentiles: 47, 56) for cases and 54 years (25th and 75th percentiles: 49, 57) for controls. The number of subjects in each age group (Supplemental Table 1) was <45 (N=815), 45 to 49 yrs (N=846), 50 to 54 (N=1,566), and 55 to 59 (N=2,005).

In Table 2, multivariable comparisons for pancreatic cancer risk are shown for EOPC and VEOPC. Consuming more than 26 g of alcohol per day (equivalent to two or more standard drinks) was associated with increased risk overall (OR 1.49, 95% CI 1.21-1.84).

The effect was stronger in the VEOPC group (<45 years, OR 2.18, 95% CI 1.17-4.09), although the interaction between alcohol and age was not statistically significant ($p=0.20$). Further, a dose-effect relationship with alcohol was apparent in all age groups (Table 3). Most notably, the risk for pancreatic cancer does not appear to increase until the threshold of 52 g (approximately 4 drinks) per day is reached in both men and women, although it was not statistically significant in women due to low numbers of participants drinking heavily. The small numbers of patients also precluded further dose-effect analyses within age subgroups. In order to determine whether the effect of alcohol on risk was only present in smokers, we analyzed the univariate effect of alcohol in the subset of never smokers alone. The effect on risk was lower than the overall univariate estimate (OR 1.61, 95% CI 1.34-1.95), consuming > 26g/day and was no longer statistically significant (OR 1.15, 95% CI 0.74-1.79), Supplemental figure 1a).

Family history of pancreatic cancer in a first-degree relative was associated with elevated risk for EOPC (OR 2.53, 95% CI 1.77-3.61) and VEOPC (OR 2.99, 95% CI 1.04-7.99) at similar levels. There was no interaction with age ($p=0.52$). Diabetes was associated with risk among EOPC (OR 1.55, 95% CI 1.16-2.06) but not in VEOPC (OR 0.85, 95% CI 0.25-2.93). There was no significant interaction with age ($p=0.84$).

As expected, cigarette smoking was also associated with elevated risk for pancreatic cancer across all age groups. According to categories of pack-years, there was a dose-response association with risk in EOPC, with the highest pack-year group (≥ 40 pack-years) showing the highest risk association overall. However, unlike alcohol, there was no evidence of an increased effect among VEOPC (OR 2.23 in VEOPC vs 2.79 overall in EOPC). There was no interaction between smoking and age ($p=0.20$).

Obesity, as reflected by body mass index ≥ 30 , was associated with increased risk of EOPC (OR 1.28, 95% CI 1.08-1.52) but not VEOPC (OR 1.13, 95% CI 0.67-1.90). There was no interaction with age ($p=0.52$). Report of pancreatitis at least 3 years prior to diagnosis/recruitment carried a high risk for EOPC (OR 4.71, 95% CI 2.03-10.93). The association did not reach statistical significance in VEOPC, but the numbers of participants with pancreatitis were small and the precision of the estimate very low (OR 2.66, 0.19-37.9).

Forest plots to investigate consistency of findings across studies are shown in Supplemental figures 1a-g. Consistent directions of positive risk association were observed across sites for cigarette smoking (1d), regular alcohol use (Figure 1), and family history of pancreatic cancer (1g), with only UCSF trending toward a protective effect). However, BMI associations appeared to vary by study (1f), with a mix of positive and negative associations. Sensitivity analyses were also performed by excluding the largest site (Mayo) from analyses, in addition to adjustment for site. The overall analyses were unchanged.

Discussion

In this pooled analysis of 1,954 pancreatic cancer cases diagnosed before age 60 (EOPC), including 226 pancreatic cancer cases diagnosed before age 45 (VEOPC), and 3,278 age- and sex-matched controls, we confirmed associations with heavy alcohol consumption,

family history of pancreatic cancer, diabetes mellitus, tobacco smoking, obesity, and pancreatitis. Heavy consumption of alcohol and family history of pancreatic cancer were somewhat more strongly associated with VEOPC than with EOPC while the association with diabetes mellitus was not observed in VEOPC.

Our results are in broad agreement with those of a large prospective study based on data from the Pancreatic Cancer Collaborative Registry⁸, which also examined associations between age of diagnosis of pancreatic cancer and various potential risk factors. A study of 25 patients with young onset (<50 years) pancreatic cancer from China found significant associations with cigarette smoking, pancreatitis and family history of pancreatic cancer.²¹ What appears key in our study is the suggestion that the association with alcohol consumption is strongest in the VEOPC group, although there is also a positive association for alcohol in the larger EOPC group.

Family history, diabetes, obesity and tobacco use are well-established risk factors for pancreatic cancer, and associations with these factors do not appear to differ between all cases and EOPC cases.^{11, 22} Certainly, alcohol appears to be less consistently associated with pancreatic cancer risk in overall studies^{13, 23, 24}, and may indeed be more important with regard to risk at a younger age, especially in higher quantities.

The effect of heavy alcohol use on risk for pancreatic cancer has been well studied, with a meta-analysis of 21 case-control studies and 11 cohort studies, including people diagnosed at all ages, reporting no increased risk in moderate drinkers (<3 drinks/day, pooled RR 0.92, 95% CI 0.86-0.97), but increased risk in those who consume ≥3 drinks daily (pooled RR 1.22, 95% CI 1.12-1.34).²⁵ With regard to an interaction with age, in an analysis of ten PanC4 case-control studies¹³, no interaction between age and alcohol consumption on risk was found.

Our findings of a dose-dependent relationship of risk with alcohol, along with the indication of greater effects of younger ages suggests that persons with the highest alcohol consumption are at increased risk of developing VEOPC and EOPC. Interestingly, only 5 of 213 (2.3%) cases reporting ≥26 g daily ethanol were diagnosed with pancreatitis at least 3 years antecedent to the pancreatic cancer diagnosis. This suggests that clinically overt pancreatitis is not necessarily the mechanism by which heavy alcohol intake increases risk.

In our study, approximately 7% of cases reported having a first degree relative affected with pancreatic cancer, a proportion similar to the 10% reported in the largest published series of VEOPC (<45 years at diagnosis)²⁶ and the 8% in the small Chinese series of patients diagnosed before age 50.²¹ The effect was marginally and non-significantly higher in the VEOPC group (OR 2.88 vs 2.52 in EOPC, Table 2). This appears slightly higher than what has been reported for pancreatic cancer overall (OR 1.76, 95% CI 1.19-2.61) in a nested case control study from cohort data.²⁷ As the causes of familial pancreatic cancer are quite heterogeneous²⁸ it is likely most practical to assess specific effects on age of onset gene by gene rather than FPC as a single entity. For instance, germline mutations in *CDKN2A*, an established high penetrance pancreatic cancer tumor suppressor gene, are not associated

with younger age at diagnosis.²⁹ Unfortunately, germline information was not available for this study.

The association between diabetes and risk for pancreatic cancer is well established.³⁰⁻³² In our study, there appeared to be no risk association for VEOPC, although there is an association in EOPC. Since we excluded diabetics diagnosed less than 3 years prior to the pancreatic cancer diagnosis in an effort to account for diabetes that is caused by pancreatic cancer^{33, 34}, this finding would be consistent with a prolonged diabetic exposure that increases the risk of developing pancreatic cancer in older ages.

Perhaps surprisingly, we did not observe a stronger smoking effect in VEOPC compared with EOPC in any pack-year category (Table 2). Several studies have demonstrated that mean age of diagnosis of pancreatic cancer is earlier in smokers than in non-smokers,^{7, 35-37} suggesting that smoking could be responsible for a larger fraction of early onset disease. In patients with hereditary pancreatitis who are at high risk of developing pancreatic cancer, smoking has been shown to be associated with a younger age of diagnosis by 20 years.³⁵ In familial pancreatic cancer kindreds, smokers developed pancreatic cancer on average 10 years earlier than non-smokers.³⁶ In sporadic pancreatic cancer, ever-smokers have been reported to develop disease on average 7 years earlier than non-smokers.³⁸ Although there is a suggestion that there is a dose-dependent relationship on age at diagnosis, with heavier smokers being the youngest at diagnosis,⁸ our results are not strongly supportive. The reasons for this are unclear, but may be related to duration of smoking exposure rather than simply intensity being important for pancreatic cancer risk, which would impact age of onset.

Obesity did not appear to have a greater effect in VEOPC compared with EOPC. One hospital-based case-control study reported that overweight or obesity, particularly during early adulthood, was associated with a younger age of diagnosis of pancreatic cancer.³⁹ However, the magnitude of the risk association seen in our EOPC group is similar to that generally reported for all ages.⁴⁰⁻⁴² There was also no statistically significant association in VEOPC, which may be due to lack of statistical power. However, obesity may increase risk of cancer by increasing inflammation, and our results suggest that (similar to smoking) many years of exposure to this subclinical inflammation are needed before the risk of pancreatic cancer is increased.

Chronic pancreatitis has been an established, if relatively rare, risk for pancreatic cancer.⁴³ In our study, there appeared to be an association with both VEOPC and EOPC. However, these results must be interpreted with caution in that pancreatitis patients were specifically excluded as controls from the Mayo Clinic study and in general chronic pancreatitis patients may be less likely to be enrolled in any study as a “healthy control.”

Limitations

Due to the large number of studies included in this analysis, there are clear potential limitations to the study. Attempts were made to review associations across studies to assess consistency. In addition, in order to prevent one study from driving the analyses too strongly

due to large numbers, adjustments were made to account for studies by site (Mayo, non-Mayo US, and external to U.S.).

Conclusions

The established risk factors for pancreatic cancer of smoking, diabetes, family history of pancreatic cancer, and obesity also apply to EOPC. VEOPC may have a differing risk profile, with indications that heavy alcohol consumption has a greater impact while diabetes, smoking and obesity are less strongly associated. Alcohol intake equivalent to four drinks or more per day had an age-dependent effect on risk, independent of tobacco use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Univariate forest plot with odds ratios and confidence intervals for daily average alcohol exposure (g ethanol/day) and risk of early onset (<age 60) pancreatic cancer in six case-control studies (MD Anderson and Ontario did not provide controls, so are not shown).

Table 1

Characteristics of PanC4 study subjects: patients with early-onset pancreatic cancer (EOPC, age < 60), the subset of EOPC patients with very early-onset pancreatic cancer (VEOPC, < age 45), and age-matched healthy controls, and the subset of controls age <45

	EOPC age < 60		VEOPC age <45		Controls age < 60		Controls age <45	
N	1,954		226		3,278		589	
<u>Study Site</u>								
Italy ¹	300		40		1197		300	
Ontario ¹	275		30		0		0	
SEARCH ¹	248		26		562		91	
LSU ²	20		3		46		2	
MD Anderson ²	101		12		0		0	
UCSF ²	165		21		602		87	
Yale ²	101		7		193		34	
Mayo Clinic ³	744		87		678		75	
	N	%	N	%	N	%	N	%
<u>Family History of PC (1st degree)</u>								
Unknown	409	21	38	17	764	23	116	20
No	1405	72	171	76	2452	75	464	79
Yes	140	7	17	8	62	2	9	2
<u>Diabetes Mellitus (DM)</u>								
Unknown	240	12	27	12	229	7	31	5
Non-DM	1577	81	193	85	2915	89	547	93
DM (< 3 years)	137	7	6	3	134	4	11	2
<u>Sex</u>								
Female	833	43	103	46	1295	40	222	38
Male	1141	58	123	54	1983	60	367	62
<u>Smoking (pack-years)</u>								
Unknown	172	9	16	7	196	6	25	4
0	569	29	79	35	1352	41	239	41
1-19	517	26	78	35	900	27	201	34

	EOPC age < 60	VEOPC age <45	Controls age < 60	Controls age <45
20-39	404	39	534	100
40+	292	14	296	24
Alcohol (g ethanol/day)				4
Unknown	484	55	217	27
< 26	1257	146	2770	530
26+	213	25	291	32
Usual BMI (kg/m ²)				5
Unknown	127	13	244	31
< 30	1366	170	2555	491
30+	461	43	479	67
Personal History of Pancreatitis (= 3 years)				11
Unknown	538	63	1403	324
No	1381	160	1867	264
Yes	35	3	8	1

Site as grouped for analysis:

- ¹ -Non-Mayo Clinic outside USA;
² -Non-Mayo Clinic inside USA;
³ -Mayo Clinic (MC)

Table 2
Odds ratios (95% CI) from multivariable adjusted logistic regression models

Variable	Value	Age <60	Age <45
N Cases/N Controls		1954/3278	226/589
Sex	Male	reference	reference
	Female	1.24 (1.08-1.42)	1.08 (0.73-1.59)
Alcohol (g ethanol/day)	< 26	reference	reference
	26+	1.49 (1.21-1.84)	2.18 (1.17-4.09)
Family History of PC	No	reference	reference
	Yes	2.53 (1.77-3.61)	2.88 (1.04-7.99)
DM Status 3 years	Non-DM	reference	reference
	DM	1.55 (1.16-2.06)	0.85 (0.25-2.93)
Smoking (pack-years)	0	reference	reference
	1-19	1.40 (1.18-1.65)	1.39 (0.90-2.16)
	20-39	2.29 (1.89-2.76)	1.87 (1.08-3.23)
	40+	2.79 (2.24-3.48)	2.23 (0.91-5.47)
Usual BMI (kg/m ²)	<30	reference	reference
	30+	1.28 (1.08-1.52)	1.13 (0.67-1.90)
Pancreatitis 3 years	No	reference	reference
	Yes	4.71 (2.03-10.9)	2.66 (0.19-37.9)

Model includes First degree Family History of Pancreas Cancer (No, Yes, Unknown), Diabetes Mellitus Status (Non-DM, DM), Gender (Male, Female), Smoking Intensity, Alcohol Consumption, Usual Adult BMI, along with an adjustment for Study Site (Non-Mayo outside USA, Non-Mayo inside USA, Mayo Clinic).

Table 3
Dose-effect analysis of alcohol on risk of pancreatic cancer in cases and controls in EOPC

Alcohol (g ethanol/day)	Equivalent (standard drinks/day)	Cases (female)	Controls (female)	Overall OR (95% CI)	Females OR (95% CI)	Males OR (95% CI)
<26	<2	1257 (587)	2770 (1150)	1.00	1.00	1.00
26-51	2-4	104 (17)	205 (31)	1.01 (0.77-1.32)	0.96 (0.50, 1.84)	0.95 (0.71, 1.28)
52-77	4-6	49 (5)	50 (8)	2.24 (1.45-3.44)	1.03 (0.31, 3.41)	2.63 (1.65, 4.21)
78-103	6-8	24 (5)	19 (3)	2.26 (1.21-4.23)	2.45 (0.56, 10.70)	2.15 (1.07, 4.34)
>104	8	36 (3)	17 (1)	4.60 (2.48-8.56)	3.58 (0.36, 35.56)	4.40 (2.30, 8.42)

Bold indicates statistical significance