

Cigar and pipe smoking, smokeless tobacco use and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (PanC4)

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Background: Cigarette smoking is the best-characterized risk factor for pancreatic cancer. However, data are limited for other tobacco smoking products and smokeless tobacco.

Materials and methods: We conducted a pooled analysis of cigar and pipe smoking and smokeless tobacco use and risk of pancreatic cancer using data from 11 case-control studies (6056 cases and 11 338 controls) within the International Pancreatic Cancer Case-Control Consortium (PanC4). Pooled odds ratios (OR) and the corresponding 95% confidence intervals (CI) were estimated by unconditional multiple logistic regression models adjusted for study center and selected covariates.

Results: Compared with never tobacco users, the OR for cigar-only smokers was 1.6 (95% CI: 1.2–2.3), i.e. comparable to that of cigarette-only smokers (OR 1.5; 95% CI 1.4–1.6). The OR was 1.1 (95% CI 0.69–1.6) for pipe-only smokers. There was some evidence of increasing risk with increasing amount of cigar smoked per day (OR 1.82 for ≥ 10 grams of tobacco), although not with duration. The OR for ever smokeless tobacco users as compared with never tobacco users was 0.98 (95% CI 0.75–1.3).

Conclusion: This collaborative analysis provides evidence that cigar smoking is associated with an excess risk of pancreatic cancer, while no significant association emerged for pipe smoking and smokeless tobacco use.

Key words: cigar, pancreatic cancer, pooled analysis, smokeless tobacco, tobacco, pipe

introduction

Cigarette smoking is the best-identified risk factor for pancreatic cancer [1–3]. A meta-analysis of 82 cohort and case-control studies [1] estimated a relative risk (RR) of 1.7 [95% confidence interval (CI) 1.6–1.9] for current smokers and 1.2 (95% CI 1.1–1.3) for former smokers, the association being consistent across geographic areas and sex.

Data for other tobacco products and pancreatic cancer risk are limited. In the above-mentioned meta-analysis, nine studies considered cigar smokers only, with the pooled RR of 1.5 (95% CI 1.02–2.3), and nine studies considered pipe smokers only, with a pooled RR of 1.4 (95% CI 0.94–2.1) [1]. Study quality tests suggested that the association was stronger for data from proxy interviews, indicating a possible role for bias.

Data are even more limited for smokeless tobacco use [4–6]. An overview of six studies from the United States and Nordic countries [5] resulted in a summary RR of 1.6 (95% CI 1.1–2.2) for ever use of any type of smokeless tobacco. In two of these

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studies, a prospective cohort study of 10 136 Norwegian men recruited in 1966 and followed up to 2001 [7], and a cohort investigation of 279 897 male Swedish construction workers [8], pancreatic cancer was the only site associated with use of snus (the main smokeless tobacco product used in Northern Europe), with RRs of 1.7 (95% CI 1.1–2.5) and 2.0 (95% CI 1.2–3.3), respectively. This association may have been related to exposure to *N*-nitroso compounds, specifically *N*-nitrosamines that may have a specific carcinogenic effect on the pancreas [5]. Associations with smokeless tobacco were less consistent in studies from North America [5], particularly in case–control studies that had a lower prevalence of use [9].

Given the relatively low exposure prevalence, the assessment of the role of tobacco products other than cigarettes requires a large sample size, typically larger than in individual studies. We conducted a pooled analysis of cigar and pipe smoking and smokeless tobacco use and pancreatic cancer risk using data from a series of case–control studies that are part of the

International Pancreatic Cancer Case-Control Consortium (PanC4) [10]. We examined the effect of cigar and pipe smoking and smokeless tobacco use, alone and in combination with cigarettes and other tobacco products.

methods

studies

In PanC4, we identified 11 case–control studies of pancreatic cancer that collected data on cigarettes and other forms of tobacco use using structured questionnaires [11–23]. Eight studies were conducted in North America [including the unpublished Louisiana School of Public Health (LSU) study] [13–21, 23], two in Europe [12, 22] and one was a multicentric study from Canada, Europe and Australia [11].

A summary description of the individual studies is presented in Table 1. Briefly, the LSU study (E. T. Fontham, unpublished data) included 69 newly diagnosed cases with primary pancreatic cancer residents of eight South Louisiana counties who were >20 years of age and 158 population-

Table 1. Summary description of individual studies included in the International Pancreatic Cancer Case-Control Consortium (PanC4) on pancreatic cancer and cigar and pipe smoking and smokeless tobacco use

Country study, reference	Study period	Cases			Controls		
		Men:women	Age range (median)	Sources	Men:women	Age range (median)	Sources
North America							
Louisiana							
LSU (E. T. Fontham, unpublished data)	2001–2006	33:36	32–86 (68)	Cancer registry	78:80	33–90 (67)	Population-based files
Minnesota							
Mayo Clinic [18]	2000–2007	624:513	29–92 (68)	Hospital	626:665	29–97 (70)	Hospital
Texas							
MDACC [15, 16]	2000–2006	539:335	28–87 (63)	Hospital	495:295	31–84 (61)	Hospital (visitors)
New York							
MSKCC [17]	2003–2008	264:245	32–89 (64)	Hospital	142:206	27–84 (58)	Hospital (visitors)
Georgia, Michigan, New Jersey							
NCI [13, 14]	1986–1989	250:243	32–79 (63)	Cancer registry	1364:782	30–81 (62)	Random digit dial (<65 years)/Health Care Financing Administration (≥65 years)
Connecticut							
Yale [23]	2005–2009	238:175	36–84 (68)	30 Connecticut hospitals + cancer registry	404:311	35–84 (68)	Random digit dial
California							
UCSF [20, 21]	1995–1999	287:240	32–85 (65)	Cancer registry	879:818	32–85 (66)	Random digit dial (<65 years)/Health Care Financing Administration as supplement for ≥65 years
Canada							
Toronto [19]	2003–2007	302:238	20–89 (65)	Cancer registry	177:136	40–79 (67)	Random digit dial
Europe							
Italy [22]	1991–2008	174:148	34–80 (63)	Hospital	348:304	34–80 (63)	Hospital
Milan [12]	1983–1999	229:133	18–86 (60)	Hospital	1140:409	21–84 (56)	Hospital
International							
Canada, Europe, Australia							
SEARCH [11]	1983–1989	447:363	32–86 (65)	Hospital, Cancer registry	858:821	28–87 (65)	Resident registry

LSU, Louisiana School of Public Health; MDACC, MD Anderson Cancer Center; MSKCC, Memorial Sloan-Kettering Cancer Center; NCI, National Cancer Institute; SEARCH, Surveillance of Environmental Aspects Related to Cancer in Humans; UCSF, University of California, San Francisco.

based controls. Controls were frequency matched to cases by age, race and gender in a 2:1 ratio. The Mayo Clinic study [18] included 1137 cases with pancreatic cancer, who were recruited between 2000 and 2007 during their visit to the Mayo Clinic (Rochester, Minnesota or Florida); controls were 1291 participants frequency matched to cases by sex, age, race and area of residence, recruited from the General Internal Medicine clinic at Mayo Clinic (Rochester). Participation rate was 62% for cases and 56% for controls. The MD Anderson Cancer Center study [15, 16] included 874 cases with cancer of the pancreas recruited between 2000 and 2006; controls were 790 participants frequency matched to cases by sex, age and race, who were selected from healthy accompanying visitors and genetically unrelated family members. Participation rate was 80% for cases and 84% for controls. The Memorial Sloan-Kettering Cancer Center (MSKCC) study [17] included 874 cases with pathologically or cytologically confirmed pancreatic adenocarcinoma; controls were 348 subjects with no personal history of cancer other than nonmelanoma skin cancer. The participation rate was 79% for cases and 59% for controls. The National Cancer Institute (NCI) study [13, 14] included 493 cases with incident adenocarcinoma of the exocrine pancreas diagnosed between 1986 and 1989 among residents in Atlanta (Georgia), Detroit (Michigan) and the state of New Jersey; controls were 2146 participants from the general population of study areas, frequency matched to cases by sex, age, race and study area, identified using random digit dial. Response rate was 45% for cases and 76% for controls. The Yale study [23] included 413 cases of pancreatic cancer and 715 population-based controls among residents of the state of Connecticut recruited between 2005 and 2009. The participation rate was 46% for cases and 63% for controls. The University of California, San Francisco (UCSF) study [20, 21] included 527 cases with incident adenocarcinoma of the exocrine pancreas who were diagnosed between 1995 and 1999. They were population-based patients identified in the six San Francisco Bay Area counties using the Northern California Cancer Center rapid case ascertainment. Controls were 1679 participants frequency matched to cases by sex and age in 5-year groups and identified from the target population using random digit dial. The participation rate of eligible cases and of controls was 67%. The Toronto study [19] included 540 cases with a first primary pathologically confirmed adenocarcinoma of the pancreas identified through the Ontario Cancer registry and 313 controls randomly selected between 2003 and 2007 using random digit dial. The Italian multicentric study [22] included 322 cases with incident pancreatic cancer (histologically, 55%, or imaging confirmed) identified between 1991 and 2008 in the major teaching and general hospitals in the provinces of Pordenone and Greater Milan and 652 hospital controls, frequency matched to cases by sex, age and area of residence. Participation rate was >95% of persons who were approached for interview. The Milan study [12] included 362 cases with incident confirmed pancreatic cancer who were admitted to the NCI and to other major hospital of Milan between 1983 and 1999, and 1149 frequency matched controls who were admitted to the same network of hospitals where cases had been identified, for acute nonneoplastic conditions. Participation rate for individuals who were approached was >95% [24]. The Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH) study [11] was a collaborative study of the International Agency for Research on Cancer including 810 cases and 1679 controls matched by age and sex collected in the 1980s in Toronto and Montreal, Canada, Utrecht, The Netherlands, Opole, Poland and Adelaide, Australia, based upon a random sample from the population at risk. Participation rate in various centers varied between 50% and 80%. Proxy interviews were obtained for ~60% of cases and 20% of controls.

A total of 6056 participants with adenocarcinoma of the exocrine pancreas and 11 338 controls were included in these present analyses. Data may differ slightly from those in published reports of the same studies due to missing data for relevant variables. Cases and controls were interviewed

in-person with the exception of the Toronto study that used self-administered questionnaires and included 63 case proxy respondents [19] and the SEARCH study [11], where proxy interviews were conducted for 474 cases and 332 controls.

The original datasets were restructured either by the original study investigators or by the central coordinators using a uniform format for data harmonization. Individual data were collected about sociodemographic characteristics, anthropometric measures, smoking and alcohol consumption, history of diabetes and of pancreatitis, family history of pancreatic cancer in first-degree relatives and histology and topography of the tumor (for cases).

exposure variables

All studies provided information on cigar and pipe smoking. Ever smokers of cigars or pipes were defined as participants who had used these products on a regular basis for at least 6 months in the LSU study and in other three studies [14, 21, 23]; who smoked at least one cigar or pipe per day for at least 1 year in two studies [12, 22]; who smoked at least one cigar or pipe per month for at least 3 months in one study [19]; or who reported to have ever smoked at least one of these products in their lifetime in the remaining five studies [11,16–18]. For cigars and pipes, the amount of daily use (grams) and duration of exposure (years) were considered when data were available (no dose nor duration data for two studies [17, 18] and duration only for the LSU study and another study [19]). Questions about ever use of smokeless tobacco were available in the LSU study and other five studies [11, 14, 16, 18, 23] of the 11 studies included in our analysis, with three studies [14, 16, 18] and the LSU study having collected data about chewing tobacco and snuff separately and, one study collecting information for chewing or snuff combined [23] and the SEARCH study [11] having collected data about chewing tobacco only. In each study, ever users of smokeless tobacco were defined as for cigar and pipe smokers described above. Information on amount of smokeless tobacco used was provided in four of the six studies [11, 14, 16, 23], while information on duration was available in all studies except one [18]. Given some inconsistencies in the definition of the measurement unit for smokeless tobacco use, it was, however, not possible to pool dose–response data across studies.

To create uniform variables across the multiple studies, one cigar or pipe full of tobacco was considered equivalent to 3 g of tobacco in European studies and to 5 g in non-European studies. For smokeless tobacco, we combined chewing and snuff in the analyses.

statistical analysis

We conducted an aggregate analysis with data from all studies pooled into a single large dataset [25]. Those who had never used any kind of tobacco were the reference category for each tobacco product. The association between cigar, pipe and smokeless tobacco use (and their combinations) and risk of pancreatic cancer was assessed by estimating the odds ratios (OR) and the corresponding 95% CI using unconditional multiple logistic regression models [26] adjusted for study center, age (<40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69 and ≥70 years), sex, education (≤eighth grade, 9th–11th grade, 12th grade or high school graduates, some college or college graduates and ≥1 year of graduate school), race/ethnicity (non-Hispanic White, Hispanic, non-Hispanic Black and others), body mass index (BMI, <20, 20 to <25, 25 to <30 and ≥30 kg/m²), history of diabetes (≥1 year before diagnosis) and total alcohol consumption (never drinkers, drinkers 1–<6 drinks/day and drinkers ≥6 drinks/day). Tests for linear trend of the ORs were based on the chi-square statistic for the exposure factor of interest when included in the model as an ordinal variable. In the analyses of tobacco smoking we excluded smokeless tobacco users, and in the analyses of smokeless tobacco use we excluded pure tobacco smokers (i.e. other tobacco products-only smokers).

results

Table 2 shows the distribution of sex, age and selected covariates for the 6056 cases and 11 338 controls for all study centers combined. Distributions of sex (56% of cases and 57% of controls were men), age (median age 65 years for cases and 64 years for controls) and racial/ethnic group (89% of cases and 84% of controls were Non-Hispanic white) were similar between cases and controls. In contrast, cases reported more years of education, a higher BMI and a more frequent history of diabetes relative to controls.

Table 3 shows the distribution and OR estimates for use of various tobacco smoking products among 5922 pancreatic cases and 11 062 controls (excluding smokeless tobacco users).

Table 2. Distribution of 6056 cases of pancreatic cancer and 11 338 controls according to sex, age, race and other selected characteristics

Characteristic	Cases, n (%)	Controls, n (%)
Sex		
Men	3387 (55.9)	6511 (57.4)
Women	2669 (44.1)	4827 (42.6)
Age (years)		
<55	1114 (18.4)	2776 (24.5)
55–64	1837 (30.3)	3222 (28.4)
65–74	2024 (33.4)	3591 (31.7)
≥75	1081 (17.9)	1749 (15.4)
Race/ethnicity		
Non-Hispanic white	5409 (89.3)	9478 (83.6)
Non-Hispanic black	356 (5.9)	1119 (9.9)
Hispanic	115 (1.9)	220 (1.9)
Others	171 (2.8)	209 (1.8)
Missing	5 (0.1)	312 (2.8)
Education		
Eighth grade or less	1044 (17.2)	2795 (24.7)
9th–11th grade	736 (12.2)	1270 (11.2)
12th grade or high school graduate	1292 (21.3)	1955 (17.2)
Some college or college graduate	1941 (32.1)	3454 (30.5)
≥1 year of graduate school	997 (16.5)	1804 (15.9)
Missing	46 (0.8)	60 (0.5)
Body mass index (kg/m²)		
<20	319 (5.3)	596 (5.3)
20 to <25	2152 (35.5)	4757 (42.0)
25 to <30	2316 (38.2)	4357 (38.4)
≥30	1191 (19.7)	1478 (13.0)
Missing	78 (1.3)	150 (1.3)
History of diabetes		
No	4651 (76.8)	10199 (90.0)
Yes	1328 (21.9)	1068 (9.4)
Missing	77 (1.3)	71 (0.6)
Alcohol drinking (drinks/day)^a		
0 to <1	3502 (57.8)	6235 (55.0)
1 to <6	1678 (27.7)	4090 (36.1)
≥6	354 (5.9)	656 (5.8)
Missing	522 (8.6)	357 (3.2)

^aNo information was available in the Memorial Sloan-Kettering Cancer Center study [17].

Compared with never tobacco users, the OR for cigarette-only smokers was 1.5 (95% CI 1.4–1.6, *P* for heterogeneity across studies = 0.0003), and for cigar-only smokers was 1.6 (95% CI 1.2–2.3, *P* for heterogeneity = 0.003). The significant

Table 3. Distribution of 5922 cases of pancreatic cancer and 11 062 controls^a, OR and corresponding 95% CI according to smoking of different tobacco products and their combinations

	Cases, n (%)	Controls, n (%)	OR ^b (95% CI)
Never tobacco users	2131 (36.0)	4599 (41.6)	1
Cigarette-only smokers	3075 (51.9)	5149 (46.6)	1.50 (1.39–1.62)
Cigar-only smokers	64 (1.1)	112 (1.0)	1.62 (1.15–2.29)
Grams of tobacco/day^c			
Never tobacco smokers	1255 (96.5)	3570 (97.4)	1
<10	22 (1.7)	64 (1.7)	1.20 (0.71–2.01)
≥10	16 (1.2)	27 (0.7)	1.82 (0.93–3.55)
Missing	8 (0.6)	6 (0.2)	
χ^2 trend; <i>P</i> -value			3.29; 0.07
Duration (years)^d			
Never tobacco smokers	1477 (96.6)	3768 (97.3)	1
<20	25 (1.6)	46 (1.2)	1.39 (0.82–2.37)
≥20	26 (1.7)	57 (1.5)	1.39 (0.83–2.32)
Missing	1 (0.1)	–	
χ^2 trend; <i>P</i> -value			2.66; 0.10
Pipe-only smokers	38 (0.6)	99 (0.9)	1.06 (0.69–1.63)
Grams of tobacco/day^c			
Never tobacco smokers	1255 (98.3)	3570 (97.8)	1
<10	11 (0.9)	41 (1.1)	0.92 (0.46–1.86)
≥10	11 (0.9)	40 (1.1)	0.78 (0.38–1.61)
Missing	–	1 (0.0)	
χ^2 trend; <i>P</i> -value			0.48; 0.49
Duration (years)^d			
Never tobacco smokers	1477 (98.1)	3768 (97.8)	1
<20	12 (0.8)	42 (1.1)	0.73 (0.37–1.46)
≥20	15 (1.0)	41 (1.1)	1.16 (0.61–2.20)
Missing	2 (0.1)	2 (0.1)	
χ^2 trend; <i>P</i> -value			0.00; 0.98
Cigarette and cigar and pipe	178 (3.0)	276 (2.5)	1.71 (1.36–2.13)
Cigarette and cigar	183 (3.1)	339 (3.1)	1.32 (1.07–1.63)
Cigarette and pipe	206 (3.5)	390 (3.5)	1.43 (1.16–1.75)
Cigar and pipe	47 (0.8)	98 (0.9)	1.13 (0.76–1.69)
Grams of tobacco/day^c			
Never tobacco smokers	1255 (98.2)	3570 (97.7)	1
<20	10 (0.8)	53 (1.5)	0.64 (0.31–1.31)
≥20	13 (1.0)	29 (0.8)	1.42 (0.70–2.85)
Missing	–	2 (0.1)	
χ^2 trend; <i>P</i> -value			0.07; 0.80

^aSmokeless tobacco users were excluded (130 cases and 267 controls).

^bEstimates from multiple logistic regression models, adjusted for center, race, sex, age, education, history of diabetes, body mass index and total alcohol consumption.

^cNo information was available in the LSU (unpublished data), Toronto [19], Mayo Clinic [18] and MSKCC [17] studies.

^dNo information was available in the Mayo Clinic [18] and MSKCC [17] studies.

CI, confidence interval; MSKCC, Memorial Sloan-Kettering Cancer Center; OR, odds ratios.

heterogeneity for cigar-only smokers was attributable to two studies with ORs below unity [17, 19] and two studies with ORs between 4 and 5 [18, 23]. For cigar-only smokers (64 cases, 112 controls), there was some evidence of increasing risk with amount of tobacco consumed per day (OR = 1.8 for ≥ 10 g/day), whereas no association was observed with duration of smoking (OR = 1.5, 95% CI 0.72–3.3 for smokers of ≥ 10 g/day of tobacco from cigars for ≥ 20 years). The OR was 1.1 (95% CI 0.69–1.6) for pipe-only smokers (P for heterogeneity = 0.01) based on 38 cases and 99 controls, with no trend in risk with increasing dose or duration. The heterogeneity in the OR for pipe-only smokers was attributed to two studies with ORs < 0.5 [13, 14, 17], and one study with an OR > 2 [19]. In analyses of combined use of various tobacco products, the OR was 1.7 for cigarette, cigar and pipe smokers; 1.3 for cigarette and cigar smokers; 1.4 for cigarette and pipe smokers and 1.1 for cigar and pipe smokers. All CIs—except for cigar and pipe smokers—excluded unity. The ORs were not meaningfully different when we excluded data from proxy respondents. The ORs were 1.5 (95% CI 1.4–1.6) for cigarette-only smokers, 1.6 (95% CI 1.1–2.3) for cigar-only smokers, 0.94 (95% CI 0.59–1.5) for pipe-only smokers, 1.7 (95% CI 1.4–2.2) for cigarette, cigar and pipe smokers, 1.3 (95% CI 0.99–1.6) for cigarette and cigar smokers, 1.4 (95% CI 1.1–1.7) for cigarette and pipe smokers, and 1.2 (95% CI 0.76–1.7) for cigar and pipe smokers.

Data for smokeless tobacco use, either alone or in combination with tobacco smoking products, and the corresponding ORs are shown in Table 4 for 1404 pancreatic cancer cases and 3014 controls (excluding tobacco smokers only). The overall OR for ever smokeless tobacco users compared with never tobacco users was 0.98 (95% CI 0.75–1.3) (P for heterogeneity across studies = 0.076). The OR was 0.62 (95% CI 0.37–1.04) for smokeless tobacco only and 1.1 (95%

CI 0.83–1.5) for users of smokeless tobacco who were also smokers (ORs ranged from 0.77 to 1.4 for various combinations of smokeless tobacco use and tobacco smoking). These results for ever smokeless tobacco use were not altered after excluding data from proxy respondents (OR = 0.98, 95% CI 0.75–1.3). There was no consistent pattern for ever smokeless tobacco use across the studies included in this pooled analysis. In the NCI study [13, 14], a significant excess risk was found for the higher frequency of use (OR = 3.84, 95% CI 1.17–12.61), while the remaining studies showed no association with pancreatic cancer, either for ever use and for more frequent and longer use (data not shown).

discussion

The large size of this collaborative analysis allowed for a more precise estimate of the association between cigar and pipe smoking and pancreatic cancer risk. Results showed that the association between cigar smoking and pancreatic cancer risk is of similar magnitude to that for cigarette smoking. The combination of cigarette with cigar or pipe smoking was associated with an excess risk of pancreatic cancer similar to that of cigarette smoking alone [1–4]. There was no evidence of an association between pancreatic cancer and pipe smoking or smokeless tobacco use, possibly on account of limited numbers of exposed subjects.

The results for cigar smokers are consistent with those of a recent meta-analysis which included only three [11,12,14] of the studies that were in our analysis [1]. However, because we pooled raw data, our analyses allowed a more detailed stratification of tobacco use and careful allowance for covariates than previously available. In particular, we were able to analyze the role of cigars, pipes and smokeless tobacco in never users of other tobacco products, thus eliminating potential residual confounding by cigarette smoking.

The same magnitude of risk for cigar and cigarette smoking is not surprising, given their similar composition. The less convincing results for pipe smoking in the present pooled analysis are consistent with those of a meta-analysis on the same issue [1].

Our results on smokeless tobacco use are in broad agreement with a recently published meta-analysis of all published data on the issue, which reported no excess risk of pancreatic cancer in case-control studies [9]. They are, however, at variance with those from another meta-analysis [5], based mainly on data from two Nordic cohort studies [7, 8], which suggested that smokeless tobacco is associated with an increased risk of pancreatic cancer. There are at least an additional case-control [27] and a cohort study [28] from the United States, showing RRs for smokeless tobacco above unity, of borderline significance. The difference in effects between our pooled analysis and the two Nordic countries may be due to differences in smokeless tobacco products used in the populations considered. Moreover, the apparent inconsistency between our findings and those from Nordic cohorts may be due to the absence of adjustment of estimates in the Nordic studies for most of the covariates allowed for in the present analyses. A US study included in our pooled analysis—despite the absence of an overall association—found an excess risk for subjects

Table 4. Distribution of 1404 cases of pancreatic cancer and 3014 controls^a, OR and the corresponding 95% CI according to use of smokeless tobacco and its combination with use of other tobacco products

	Cases, <i>n</i> (%)	Controls, <i>n</i> (%)	OR ^b (95% CI)
Never tobacco users	1274 (90.7)	2747 (91.1)	1
Ever smokeless tobacco users	130 (9.3)	267 (8.9)	0.98 (0.75–1.27)
Smokeless tobacco-only users	23 (1.6)	63 (2.1)	0.62 (0.37–1.04)
Smokeless tobacco users and cigarette	63 (4.5)	94 (3.1)	1.36 (0.94–1.96)
Smokeless tobacco users and cigar and pipe	11 (0.8)	21 (0.7)	1.44 (0.65–3.21)
Smokeless tobacco users and cigarette and cigar or pipe	33 (2.4)	89 (3.0)	0.77 (0.49–1.21)

^aTobacco smokers only were excluded (4648 cases and 8315 controls). No information on smokeless tobacco was available in the Milan [12], Italy [22], University of California, San Francisco [20, 21], Toronto [19] and Memorial Sloan-Kettering Cancer Center [17] studies.

^bEstimates from multiple logistic regression models, adjusted for center, race, sex, age, education, history of diabetes, body mass index and total alcohol consumption.

CI, confidence interval; OR, odds ratio.

consuming >2.5 ounces/week of smokeless tobacco [14], while there was no evidence of an excess risk for higher use in the remaining studies providing information on dose.

Although the present results for smokeless tobacco can be due to the low frequency of smokeless tobacco in populations other than Nordic countries, the present data suggest the absence of any dose–risk relation with smokeless tobacco. Further, we were able to allow for study design variables and major identified possible confounding factors, including ethnicity, education, BMI, diabetes and alcohol consumption [29], and to estimate the risk of smokeless tobacco use in lifelong nonsmokers, thus minimizing any possible bias due to residual confounding.

Study design issues, such as use of hospital-based or population-based controls, could not be adequately assessed due to the small numbers of exposed participants. It is possible that hospital controls include some diagnoses related to tobacco use that would lead to an underestimation of the true association. However, results from a recent meta-analysis on tobacco smoking and pancreatic cancer risk [1] do not support this, showing RR estimates to be higher in hospital-based case–control studies than in population-based ones and RRs of similar magnitude in cohort and case–control studies [1]. Thus, for current pipe and cigar smokers, the RR was 1.24 (95% CI 0.82–1.86) for population-based case–control studies and 1.94 (95% CI 1.15–3.28) for hospital-based ones, 1.37 (95% CI 0.90–2.08) for cohort studies and 1.52 (95% CI 1.09–2.12) for case–control studies. Interestingly, the pooled OR for cigarette smokers in our study population was consistent with that of previous cohort studies [1–3]. Tobacco consumption is frequently underreported [30] and this may have biased our results, particularly if recall bias and misclassification differed between cases and controls. However, the similarities of our findings with those from cohort studies argue against a major role of recall bias and misclassification, which are also unlikely to differ by type of tobacco product.

In conclusion, this large collaborative pooled analysis of nongigarette tobacco use in 11 studies within PanC4 provides evidence that cigar smoking is associated with an excess risk of pancreatic cancer, while, based on small numbers, no significant association emerged for pipe smoking and smokeless tobacco use.

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disclosure

The authors have declared no conflicts of interest.

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