Smoking and Pancreatic Cancer in Men and Women[1]

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Abstract

Most studies of smoking and pancreatic cancer have used male subjects or combined men and women together in statistical analyses. There is little information on the relative risk of smoking and pancreatic cancer in women. Because of the high case-fatality rate, many of these studies were also based on information gathered from proxy respondents, in which smoking habits may not be recalled with certainty. A hospital-based study of 484 male and female patients with pancreatic cancer and 954 control subjects was conducted based on direct interviews of incident cases. Compared to never smokers, the odds ratio (OR) for current cigarette smokers was 1.6 [95% confidence interval (CI), 1.1–2.4] for men and 2.3 (95% CI, 1.4–3.5) for women. In women, but not in men, there was a trend in the ORs with years of daily cigarette consumption ($P < 0.01$). Filter cigarettes offered no protective advantage compared to nonfilter cigarettes. Among men, the OR was 2.1 (95% CI, 1.2–3.8) for pipe/cigar smokers and 3.6 (95% CI, 1.0–12.8) for tobacco chewers. Tobacco smoke causes pancreatic cancer when inhaled into the lungs. Tobacco juice may also cause pancreatic cancer when ingested or absorbed through the oral cavity. These data suggest that smoking is a cause of pancreatic cancer in women and that the risks for female smokers are comparable to male smokers. Nevertheless, the causes of most pancreatic cancers are unknown.

Introduction

The pathogenesis of pancreatic carcinoma is not well understood. Only cigarette smoking has been consistently reported as a risk factor, although its effects are relatively weak. Although most studies of smoking and pancreas cancer found approximately 1.5–2-fold increased risks (1–24), other reports found no effect (25, 26). With few exceptions, the effects of cigarette smoking have not been examined separately by gender. Because pancreas cancer is a relatively rare disease, risk estimates have usually been based on male subjects or on male and female subjects combined. We examined the effects of cigarette smoking on pancreatic cancer using a large case-control study based on direct interviews. The effects of pipes, cigars, and smokeless tobacco are also examined.

Materials and Methods

Because of the high case-fatality rate, many case-control studies of pancreatic cancer obtained exposure information from the next-of-kin. Furthermore, the response rates from population-based case-control studies in general are usually lower than those from hospital-based studies. To minimize potential information and selection biases, a hospital-based study of pancreatic cancer (International Classification of Disease Codes, 9th Revision, code 157.0) was conducted in New York City and other locations (see "Acknowledgments") that obtained exposure information directly from patients. Daily hospital admission logs were screened to ascertain newly diagnosed incident cases of pancreatic cancer who were between the ages of 21 and 80. The pathology report of each clinically diagnosed case was examined to confirm the admitting diagnosis, and only subjects with a histological confirmation were eligible for entry into the study. Four hundred and eighty-four patients with pancreatic carcinoma and 954 control subjects were interviewed between 1985 and 1993 by trained interviewers. Controls were patients who did not have pancreatic cancer and were hospitalized for conditions unrelated to tobacco use. Among men, the control diagnoses were: cancer (soft tissue, melanoma, lymphoma, and leukemia), 34.8%; musculoskeletal conditions, 9.3%; benign prostatic hypertrophy, 12.6%; other benign conditions, 6.6%; injuries/fractures, 7%; and all other diagnoses (nonmalignant diseases of the nervous system, urinary conditions, skin disorders, ill-defined symptoms, congenital disorders, and others), 29.7%. Among women, the control diagnoses were: cancer (soft tissue, melanoma, lymphoma, and leukemia), 27.7%; benign tumors, 8.9%; musculoskeletal conditions, 16.4%; injuries/fractures, 12%; and all other conditions (pelvic disorders, benign breast disease, skin conditions, urinary disorders, and others), 35%. The control subjects were matched to cases by hospital, sex, age (± 5 years), race, and year of diagnosis. Two controls were selected for each case. Of the 949 eligible cases who were approached, 10 (1%) had died, and 373 (39.3%) were either too ill or unable to communicate, 15 (1.6%) were physician refusals, and 67 were patient refusals (7.1%). Control selection was accomplished by approaching the first eligible patient fitting the study needs listed on the daily hospital admission sheets. In case of refusal, the patient with the next sequential admission on the daily admission sheets with an acceptable diagnosis was approached. Of the 1526 eligible controls who were approached, 357 (23.3%) were either too ill or unable to communicate, 6 (0.4%) had died, 122 (8.0%) were physician refusals, and 87 (5.7%) were patient refusals. Written informed consent was obtained from all patients. The questionnaire included detailed sections on demographics, tobacco smoking, alcohol consumption, occupation and occupational exposures, weight, height, and medical history of illness and disease.

Current smoking was defined as having smoked at least

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Table 1 Sociodemographic characteristics of pancreatic cancer cases and controls, 1985–1993

	Males		Females	
	Cases	Controls	Cases	Controls
	(*N* = 290) %	(*N* = 572) %	(*N* = 194) %	(*N* = 382) %
Age				
<45	7.3	8.0	4.6	7.1
45–54	17.9	18.4	15.5	14.7
55–64	36.2	37.4	33.0	36.7
65–74	32.1	29.6	36.6	34.3
75+	6.5	6.6	10.3	7.3
Years of education				
<12	17.2	15.9	16.5	21.5
12	26.9	24.3	39.2	35.4
13–15	19.0	19.1	25.8	21.5
16+	36.9	40.7	18.6	21.5
Race				
White	94.8	95.6	90.2	91.1
Black	4.5	4.0	9.3	8.6
Other	0.7	0.3	0.5	0.3
Religion				
Protestant	22.4	26.8	31.4	31.2
Catholic	48.6	47.7	39.2	45.3
Jewish	24.8	23.8	26.8	22.0
Other/None	4.0	4.0	2.6	1.5

one cigarette/day in the year preceding the current diagnosis. Ex-smokers were quitters who had not smoked within the past year. Descriptive statistical methods included frequency tables and χ^2 analysis. ORs[3] from multiple logistic regression coefficients and 95% CIs were obtained after adjustment for age and education. The effects of possible confounders including alcohol consumption, body weight, and diabetes were assessed by changes in deviance in the models. The fit of the model was evaluated by the Hosmer and Lemeshow test (27). All trend tests were performed by treating the main effect as continuous response variables and assigning the median value to each category of exposure.

Results

Information on the site of the cancer in the pancreas was available for 231 (48%) patients. The distribution of the tumor site was: head, 83%; body, 13%; and tail, 4%. The male:female ratio of case subjects was 1.5. There were little differences in age, race, and religious status between cases and control patients (Table 1). The mean age was 61 for male cases, 60 for male controls, and 62 for both female cases and controls. The average number of years of education was 14 for both male cases and controls and 13 for both female cases and controls.

Twenty-nine percent of male cases and 22% of male controls were current cigarette smokers. In women, 28% of cases and 19% of controls were current smokers. The age-adjusted OR for pancreatic cancer among current smokers was 1.6 (95% CI, 1.1–2.4) for men and 2.3 (95% CI, 1.4–3.5) for women compared to men and women who never smoked tobacco, respectively (Table 2). In the subgroup of case patients with cancer in the pancreas head, the adjusted OR was 1.9 (95% CI, 1.1–3.3) in men and 1.6 (95% CI, 0.9–3.0) in women. In patients with cancer in the body, tail, or pancreatic duct, the OR was 1.2 (95% CI, 0.4–3.2) in men and 4.8 (95% CI, 1.4–16.2) in women. Among all patients who currently smoked cigarettes, the risk increased with the number of cigarettes smoked per day. The OR for smokers of 20–39 cigarettes/day was 1.4 (95% CI, 0.7–2.8) in men and 2.3 (95% CI, 0.8–6.3) in women. For 2 or more packs/day, the OR was 1.8 (95% CI, 0.9–3.6) in men and 5.6 (95% CI, 2.0–15.8) in women.

In ex-smokers, there was no increased risk among men, whereas the OR for women was 1.9 (95% CI, 1.3–2.9). The OR for men and women who quit within 2 years was actually higher than for current smokers, especially in women. The risk estimates were 1.7 (95% CI, 0.8–3.7) in men and 10.6 (95% CI, 2.9–39.2) in women; these findings could reflect that some patients quit smoking with the onset of clinical symptoms. In the subgroup of patients with cancer in the head of the pancreas, the OR in quitters was 1.0 (95% CI, 0.6–1.8) in men and 1.4 (95% CI, 0.7–2.5) in women. In patients with cancer in the body, tail, or pancreatic duct, the OR was 0.7 (95% CI, 0.3–1.8) in men and 3.2 (95% CI, 1.0–10.6) in women.

When examining the risk by duration, there was a significant trend with increasing number of years of smoking in women but not in men. The risk estimates were higher for women than for men in each duration category of smoking (Table 2). Male patients who smoked 40 or more years had a 1.3 (95% CI, 0.8–2.1)-fold risk of pancreatic cancer, compared to a 2.1 (95% CI 1.3–3.4)-fold risk for women. The OR for smoking nonfilter cigarettes compared to filter cigarettes was 0.7 (95% CI, 0.3–1.9) for men and 1.5 (95% CI, 0.3–8.9) for women.

Among men, the adjusted OR was 1.8 (95% CI, 0.9–5.3) for smoking pipes only compared to both never and long-term quitters (>20 years) combined. The average number of pipes smoked per day was 6.3 for cases and 6.7 for controls. There was no trend in the OR with the duration of pipe smoking (Table 3). The OR for smoking cigars only was 3.1 (95% CI, 1.4–6.9) compared to never and former cigarette smokers. The mean number of cigars smoked per day was 4 for cases and 3 for controls. There was no trend in the ORs with duration of smoking cigars. There were six male cases and five male controls who chewed tobacco regularly for at least 1 year and did not currently smoke cigarettes. The crude OR for these tobacco chewers compared to never and long-term quitters was 3.6 (95% CI, 1.0–12.8). There were no women who reported chewing tobacco or smoking pipes and cigars. Only two male cases and three male controls reported using snuff for at least 1 year.

Discussion

The male:female ratio of 1.5:1 in white subjects in this study is similar to the rate ratio in the United States as well as in most other Western and Asian countries, suggesting a common etiology in many populations. Cigarette smoking has been identified as a cause of pancreas cancer in most epidemiological studies of pancreatic carcinoma, although few studies reported specific risk estimates for women. Because pancreatic cancer is relatively uncommon, most studies have been based only on male subjects or have combined men and women in statistical analyses. Our data indicate that smoking is a cause of pancreatic cancer in women and that the risks in women are somewhat higher than in men for categories of amount and duration of smoking. Somewhat similar findings were observed in another large population-based study based on direct interviews. In an

[3] The abbreviations used are: OR, odds ratio; CI, confidence interval; TSNA, tobacco-specific *N*-nitrosamines; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

Table 2 ORs for pancreatic cancer by tobacco smoking

Smoking status	Males			Females		
	Cases (*N* = 290)	Controls (*N* = 572)	OR[a] (95% CI)	Cases (*N* = 194)	Controls (*N* = 382)	OR[a] (95% CI)
Tobacco smoking						
Never	66	157	1.0	78	221	1.0
Current smokers	85	127	1.6 (1.1–2.4)	54	73	2.3 (1.4–3.5)
Ex-smoker	114	260	1.0 (0.7–1.5)	62	88	1.9 (1.3–2.9)
Pipe/cigar	25	28	2.1 (1.2–3.8)	0.0	0.0	
Cigarettes smoked/day (current smokers)						
0	66	157	1.0	78	221	1.0
1–19	48	73	1.5 (0.9–2.4)	37	55	2.1 (1.3–3.6)
20–39	16	27	1.4 (0.7–2.8)	7	11	2.3 (0.8–6.3)
40+	21	27	1.8 (0.9–3.6)	10	7	5.6 (2.0–15.8)
Smoking yrs						
0	66	157	1.0	78	221	1.0
1–9	15	47	0.8 (0.4–1.5)	6	13	1.3 (0.5–3.6)
10–19	27	62	1.0 (0.6–1.8)	11	20	1.7 (0.8–3.7)
20–29	45	85	1.3 (0.8–2.0)	26	33	2.4 (1.3–4.4)
30–39	58	98	1.4 (0.9–2.2)	38	49	2.2 (1.4–3.7)
≥40	54	95	1.3 (0.8–2.1)	35	46	2.1 (1.3–3.4)
P for trend			<0.14			<0.01
Yrs since quitting (ex-smokers)						
0	66	157	1.0	78	221	1.0
1–2	12	17	1.7 (0.8–3.7)	11	3	10.6 (2.9–39.2)
3–5	7	35	0.5 (0.2–1.1)	8	15	1.5 (0.6–3.7)
6–10	15	31	1.2 (0.6–2.3)	12	17	2.1 (0.9–4.5)
>10	80	177	1.1 (0.7–1.6)	31	53	1.6 (1.0–2.7)
P for trend			NS			<0.05
Cigarette filter status[b] (current smokers)						
Filter only	23	28	1.0	18	27	1.0
Filter ≥20 yrs	32	53	0.7 (0.3–1.3)	21	31	0.6 (0.3–1.7)
Filter 1–19 yrs	17	28	0.8 (0.3–1.4)	11	11	1.1 (0.4–3.3)
Nonfilter only	10	15	0.7 (0.3–1.9)	4	3	1.5 (0.3–8.9)

[a] All ORs were adjusted for age and education. Terms for alcohol were statistically significant in the model examining duration of smoking in men. NS, not significant.
[b] ORs were also adjusted for cigarettes/day. Information on filter status was missing for six men and one woman.

analysis of 526 cases and 2153 controls, Silverman *et al.* (23) found a higher relative risk for women than for men in subjects who smoked 20 or more years (OR = 2.1 for women, 1.7 for men). Also similar to our findings, this group observed a dose-dependent effect of smoking and a reduced risk associated with smoking cessation. Using mostly next-of-kin interviews from 490 pancreatic cancer patients and controls, Mack *et al.* (11) calculated ORs of 6.0 for women and 5.3 for men who currently smoked more than one pack daily. In Shanghai, China, Ji *et al.* (24) found similar ORs for men (1.6; 95% CI, 1.1–2.2) and women (1.4; 95% CI, 0.9–2.4) who currently smoked. Clavel *et al.* (25) found no association between smoking and pancreatic cancer in both men and in women. Two other reports with separate risk estimates for men and women were based on few cases or combined smokers and ex-smokers together in the analysis (26, 9). The slightly higher smoking-related risks in women may be due to an effect of smoking in the body or tail of the pancreas. Although we had information on the site of cancer within the pancreas for only half of the patients, smoking was related to an increased risk for the body, tail, and pancreatic duct in women but not in men. Additional studies are needed to confirm this observation.

Our study and the study by Silverman *et al.* (23) show that switching from a nonfilter cigarette to a filter cigarette did not lower the risk of pancreatic cancer. Cigarette filters reduce the concentration of inhaled particulate matter containing the carcinogenic polycyclic aromatic hydrocarbons. Tobacco smoke also contains TSNAs (28). The concentration of TSNAs is not reduced in the smoke of filter cigarettes compared to nonfilter cigarettes. This suggests that TSNAs are possibly the responsible agents in tobacco that cause pancreatic cancer. Experimental studies have shown that the TSNAs NNK and NNAL are the only tobacco components known to cause cancer of the exocrine pancreas in animals (29). Chewing tobacco contains significant amounts of tobacco-specific nitrosamines (30). Elevated rates of pancreatic cancer among chewers of smokeless tobacco have been observed in some populations (31), and significant associations were found in case-control (8) and cohort studies (19). Our data suggest an association with use of chewing tobacco, although there were few tobacco chewers in this study. We found a significant increased risk for pipe and cigar smokers, who have the tendency not to inhale the smoke, although there was no significant trend with duration of smoking. The increased risk associated with pipes and cigars is consistent with earlier findings, however (1, 2). The different forms of tobacco that are associated with pancreatic cancer suggest that the TSNAs in tobacco smoke can affect the pancreas by inhalation into the lungs, absorption through the oral cavity, or ingestion.

Alternatively, nicotine in cigarette smoke may be involved

Table 3 ORs for pancreatic cancer by pipe and cigar smoking in men

Smoking status	Cases	Controls	OR (95% CI)[a]
	N	*N*	
Pipe smoking			
0	146	334	1.0
1–20 yrs	6	7	1.8 (0.6–5.3)
>20 yrs	10	13	1.6 (0.7–3.7)
Pipes smoked/day			
0	146	334	1.0
1–5	7	10	1.4 (0.5–3.8)
≥6	9	10	1.4 (0.9–2.2)
Cigar smoking			
0	146	334	1.0
1–20 yrs	7	4	3.9 (1.2–13.6)
>20 yrs	8	7	2.2 (0.8–7.3)
Cigars smoked/day			
0	146	334	1.0
1–4	8	11	1.4 (0.6–3.6)
≥5	7	1	14.1 (1.7–115.7)

[a] ORs for pipe and cigar smokers were adjusted for age and education. Baseline groups include never smokers and long-term (>20 years) quitters.

in the postinitiation stage of pancreatic cancer. Nicotine in drinking water slightly increases the incidence of pancreatic tumors in experimental animal studies (32) and inhibits apoptosis in normal and transformed cells caused by tobacco use (33).

The results from this study should be interpreted within the confines of case-control biases such as choice of hospital controls, recall bias, and confounders. There may be hospital-referral patterns that result in selection bias. For example, the male:female ratio in black subjects was 0.7, compared to 1.5 for white subjects. In one of the participating hospitals, 75% of cases resided in New York or New Jersey, compared to 85% of controls ($P < 0.01$), although there were no significant case-control differences in county of residence within states. There were no case-control differences in state of residency in other participating centers. Selection bias resulting in an underestimate of the smoking-related relative risks may have resulted from the inability to obtain smoking information from deceased or critically ill patients. These patients may have been the heaviest smokers. However, the smoking-related risks of pancreatic cancer in cohort studies (3, 4) are similar to those found in the current study. It has also been suggested that the prevalence of smoking in hospital controls is higher than in the general population (34). However, studies by our group comparing the smoking prevalence rates in the neighborhoods of the participating hospitals reveal a higher smoking prevalence rate than in our hospital control population, showing that exclusion of control subjects with tobacco-related diseases is a successful strategy for reducing selection bias (35). In male controls, the smoking prevalence ranged from 14% in the patients with sarcomas and 16% in the patients with skin cancer to 50% in the patients with spinal and back problems. In female controls, the groups with the lowest smoking prevalence were arthritic patients (8.8%) and fracture patients (16%). The highest prevalence of smoking was in women admitted for back problems (27%). Because the etiology of pancreas cancer remains largely unknown, our findings could have been confounded by other possible factors such as dietary fat or other unknown exposures.

It has been suggested previously that carcinogens present in the bile may explain the predominance of pancreatic cancers in the head of the pancreas by reflux of bile into the proximal pancreatic duct or pancreatic arterioles (6, 7). The tobacco-specific nitrosamines NNK and NNAL are metabolically activated in the liver and excreted into the bile. NNK metabolites have been detected and measured in the bile of rats after i.p. administration of NNK (36). The higher rate of pancreas cancer in smokers and tobacco chewers and the production of pancreatic tumors in laboratory animals after NNK and NNAL administration suggest that this compound may be a carcinogen for the human pancreas (37). However, the epidemiology of pancreas cancer indicates that tobacco is a relatively weak pancreas carcinogen.

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