Smokeless and Other Noncigarette Tobacco Use and Pancreatic Cancer: A Case-Control Study Based on Direct Interviews

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Abstract

Cigarette smoking is an important and well-established cause of pancreatic cancer. In contrast, little is known about the effects of smoking cigars, pipes, and use of smokeless tobacco on pancreatic cancer risk. The objective of the present study was to examine the association between noncigarette tobacco use (*i.e.*, cigars, pipes, smokeless tobacco) and pancreatic cancer risk among nonsmokers of cigarettes. A population-based case-control study of pancreatic cancer was conducted during 1986–1989 among residents of Atlanta, Georgia, Detroit, Michigan,, and 10 counties in New Jersey. Direct interviews were successfully completed with 526 newly diagnosed pancreatic cancer patients and 2153 controls ages 30–79 years. This analysis was restricted to lifelong nonsmokers of cigarettes and based on interviews with 154 cases newly diagnosed with carcinoma of the exocrine pancreas and 844 population controls who reported no history of cigarette smoking. We observed a consistent pattern of increased risk associated with cigar smoking, although these elevations were not statistically significant. Participants who smoked cigars regularly (*i.e.*, at least one cigar/week for ≥6 months) experienced a 70% increased risk [95% confidence interval (CI): 0.9–3.3], and those who never used other form of tobacco had a 90% increased risk (95% CI: 0.8–4.3). Risk was elevated among those who smoked more than one cigar/day [odds ratio (OR) = 1.8; 95% CI: 0.8–4.2) and among those who smoked cigars > 20 years (OR = 1.9; 95% CI: 0.9–3.9). Trends in risk with increasing amount and duration smoked were consistent but not statistically significant ($P = 0.17$ and $P = 0.16$, respectively). Subjects who used smokeless tobacco regularly had a 40% increased risk of pancreatic cancer (95% CI: 0.5–3.6) compared with nonusers of tobacco. We observed a marginally significant increasing risk with increased use of smokeless tobacco ($P = 0.04$); participants who used >2.5 oz of smokeless tobacco a week had an OR of 3.5 (95% CI: 1.1–11). Long-term use of smokeless tobacco (*i.e.*, >20 years) was also associated with a nonsignificant increased risk (OR = 1.5; 95% CI: 0.6–4.0). In contrast, pipe smokers experienced no increased risk (OR = 0.6; 95% CI: 0.1–2.8). Our results suggest that heavy use of smokeless tobacco, and to a lesser extent, cigar smoking may increase the risk of pancreatic cancer among nonsmokers of cigarettes.

Introduction

Noncigarette tobacco use has been increasing in the United States since the early 1990s (1, 2), heightening awareness of the health effects of use of noncigarette tobacco. Recent results from the American Cancer Society Prospective Cancer Prevention Study suggest that men who smoked cigars, but not cigarettes or pipes, are at increased risk of several sites of cancer known to be associated to cigarette consumption, including lung, esophagus, larynx, oral cavity, and possibly pancreas (3). Cigarette smoking is an important and well-established cause of pancreatic cancer. In contrast, little is known about the effect of noncigarette tobacco use on pancreatic cancer risk. Studies of the noncigarette tobacco use pancreatic cancer association have been hampered by the relatively few nonsmokers of cigarettes who used other forms of tobacco. Exclusion of cigarette smokers from such studies is important to estimate the independent effect of noncigarette tobacco use. Additional limitations of most case-control studies of pancreatic cancer include misclassification of disease and low response rates because of the rapid fatality from this disease (4–6). Patterns of risk by type of tobacco use coupled with information about differences in the putative carcinogens present in these types of tobacco may help to identify the human pancreatic carcinogens present in tobacco. The purpose of our study was to estimate the risk of pancreatic cancer associated with smoking cigars, pipes, and use of smokeless tobacco.

Materials and Methods

Detailed methods have been described previously (5). Briefly, this population-based case-control study was initiated simultaneously with case-control studies of three other malignancies (*i.e.*, esophagus, prostate, and multiple myeloma). The case series included all cases of carcinoma of the exocrine pancreas (International Classification of Diseases for Oncology code = 157) newly diagnosed from August 1986 through April 1989 among 30–79-year-old residents of geographic areas covered by population-based cancer registries located in Atlanta, Georgia (DeKalb and Fulton counties); Detroit, Michigan (Macomb, Oakland, and Wayne counties); and the state of New Jersey (10 counties). Despite a relatively short median time from diagnosis to interview (7 weeks), 471 of the 1153 patients initially iden-

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Table 1 Risk of pancreatic cancer by tobacco type among nonsmokers of cigarettes

Type of tobacco	No. of cases	No. of controls	Adjusted odds ratio[a]	(95% confidence interval)
Nonusers of tobacco	123	682	1.0	
Cigars				
Ever cigars	16	85	1.7	(0.9–3.3)
Only cigars	9	37	1.9	(0.8–4.3)
Pipes				
Ever pipes	9	62	0.6	(0.1–2.8)
Only pipes	1	24	0.3	(0.04–2.4)
Smokeless tobacco				
Ever used smokeless tobacco	7	44	1.4	(0.5–3.6)
Only used smokeless tobacco	5	28	1.1	(0.4–3.1)

[a] Cigarette smokers excluded. Adjusted by race, gender, geographic site, cigar smoking, smokeless tobacco, and age.

tified for study died before the interview could be conducted. Of the 682 surviving patients identified for study, 526 (77%) case patients were interviewed.

The control series was drawn from the general population of the study areas, frequency-matching controls to the expected age-race-gender distribution of cases of all four types of cancer combined in each study area. Controls 30–64 years old were selected by random-digit dialing. Of the 17,746 households telephoned, 86% provided a household census that served as the sampling frame for selection of controls under age 65 years. Of the 1568 controls chosen from these households, we interviewed 1227 (78%). Controls ages 65–79 years consisted of a stratified random sample drawn from The Centers for Medicare and Medicaid Services (formerly Health Care Financing Administration) rosters of the population age ≥ 65 years in each study area. Of the 1232 older controls selected, we interviewed 926 (75%).

We excluded from analysis 32 cases who were unlikely to have adenocarcinoma of the exocrine pancreas and 13 cases and 54 controls with unsatisfactory interviews. All cigarette smokers (327 cases and 1255 controls) were also excluded from this analysis. Thus, the analysis was based on first person interviews with 154 cases with a diagnosis of carcinoma of the exocrine pancreas and 844 population controls who were lifelong nonsmokers of cigarettes. The study was reviewed and approved by the institutional review board of the National Cancer Institute.

Cigar smokers were defined as subjects who reported smoking at least one cigar/week for at least 6 months. The same 6-month requirement (one pipe/week, chewed one pouch or plug/week, or ever used snuff) was used to define regular users of pipes, chewing tobacco, and snuff, respectively. Because of the small number of users of chewing tobacco and snuff and the high correlation between them, we combined use of chewing tobacco and/or snuff into one smokeless tobacco use variable. The amount of chewing tobacco and snuff was combined onto ounces of smokeless tobacco with each can of snuff contributing 1.2 oz of tobacco and each unit of chewing tobacco contributing 3 oz (pouches) or 2.33 oz (plugs) of tobacco. We defined nonusers of tobacco as subjects who reported not using any type of tobacco product.

Odds ratio (OR) and 95% confidence intervals (CIs) were estimated by unconditional logistic regression analysis (7). Statistical models included terms for exposure (*i.e.*, cigar smoking, pipe smoking, and smokeless tobacco), matching factors (*i.e.*, age at diagnosis/interview, race, gender, and study area), as well as potential confounding factors (*i.e.*, ever smoked cigars and ever used smokeless tobacco). Additional potential confounders [*i.e.*, diabetes mellitus (diagnosed at least 5 years before the diagnosis of cancer), alcohol, gallbladder disease, income, obesity, marital status, total calories, and pipe smoking] did not substantially modify any of the risk estimates and were not included in the final models. To test for linear trend, we computed the Wald statistic. The exposure variable was treated as continuous in the model by entering the median value for each level of the categorical variable among the controls.

Results

Table 1 shows risk estimates for use of each type of tobacco (*i.e.*, cigars, pipes, and smokeless tobacco). Cigar smokers had an OR of 1.7 (95% CI: 0.9–3.3), and cigar smokers who never used other form of tobacco had an OR of 1.9 (95% CI: 0.8–4.3). Consistent positive trends in risk with both amount and duration smoked cigars were apparent, although these trends were not statistically significant ($P = 0.17$ and $P = 0.16$, respectively; Table 2). Risk was elevated among those who smoked more than one cigar/day (OR = 1.8; 95% CI: 0.8–4.2) and among those who smoked cigars > 20 years (OR = 1.9; 95% CI: 0.9–3.9).

Use of cigars and pipes was highly correlated. Most pipe smokers also smoked cigars. Those who ever smoked cigars but never smoked pipes had a higher risk (OR = 1.5; 95% CI: 0.7–3.5) than those who ever smoked pipes and never smoked cigars (OR = 0.7; 95% CI: 0.2–3.0). Risk estimates for cigar smokers were affected little by adjustment for pipe smoking (OR = 1.7; 95% CI: 0.8–3.5), but those for pipe smoking were close to the unity after cigar smoking was taken into account. After adjustment for cigar smoking and smokeless tobacco use, ORs were as follows: ever smoked pipes regularly 0.6 (95% CI: 0.1–2.8); smoked pipes > 20 years 0.8 (95% CI: 0.2–3.7); and smoked more than two pipe fills/day 0.7 (95% CI: 0.1–3.5).

Subjects who ever used smokeless tobacco and never smoked cigarettes had a 40% increased risk of pancreatic cancer (95% CI: 0.5–3.6) compared with nonusers of any tobacco product (Table 1). We observed a marginally significant increasing risk with increased use of smokeless tobacco ($P = 0.04$); subjects who used >2.5 oz of smokeless tobacco a week had an OR of 3.5 (95% CI: 1.1–11; Table 2). Long-term users of smokeless tobacco had an OR of 1.5 (95% CI: 0.6–4.0), but the trend in risk with duration of use was not significant ($P = 0.42$). Although use of chewing tobacco and snuff were highly correlated, chewing tobacco use seemed to contribute more than snuff use to the observed increased risk of pancreatic cancer among users of smokeless tobacco. When we included both types of smokeless tobacco in the same model adjusting for cigar smoking, the resulting ORs were 1.7 (95% CI: 0.6–

Table 2 Numbers of cases and controls and odds ratios by amount and years smoked cigars and smokeless tobacco among nonsmokers of cigarettes

Type of tobacco	No. of cases	No. of controls	Adjusted (odds ratio)[a]	(95% CI)	*P* for trend
Nonusers of tobacco	123	682		1.0	
Cigars					
Cigars smoked/day					
≤1	7	41	1.6	(0.7–4.1)	
>1	9	41	1.8	(0.8–4.2)	0.17
No. of years smoked					
≤20	3	24	1.2	(0.3–4.3)	
>20	13	61	1.9	(0.9–3.9)	0.16
Smokeless tobacco					
Ounces/wk					
≤2.5	1	22	0.3	(0.04–2.5)	
>2.5	6	22	3.5	(1.1–10.6)	0.04
No. of years used					
≤20	1	10	1.1	(0.1–11.0)	
>20	6	33	1.5	(0.6–4.0)	0.42

[a] Cigarette smokers were excluded. Adjusted by race, gender, geographic site, and cigar smoking, smokeless tobacco, and age.

4.5) and 1.1 (95% CI: 0.4–3.5) for chewing tobacco and for snuff use, respectively. Subjects who chewed tobacco used more ounces of smokeless tobacco/week (mean of 7.2 oz) than those who dipped snuff (2.4 oz) and experienced a marginally significant increasing risk of pancreatic cancer with increased use of chewing tobacco ($P = 0.04$).

Additional analyses including cigarette smokers indicated patterns of risk similar to those observed for nonsmokers of cigarettes.

Discussion

Our results suggest that heavy use of smokeless tobacco and, to a lesser extent, cigar smoking may increase the risk of pancreatic cancer among nonsmokers of cigarettes.

Results of studies of the relation between cigar smoking and pancreatic cancer have been equivocal. Increased pancreatic cancer risk has been reported for cigar smokers in some prospective (2, 3, 8, 9) and retrospective studies (10–12) but not all (13, 14). Most studies with positive findings presented risks for smoking only cigars, whereas most negative studies included cigarette smokers in their analyses or did not report the effects of smoking only cigars.

Our study is the first positive report of the effect of smokeless tobacco on pancreatic cancer risk among noncigarette smokers. Increased risk for users of smokeless tobacco was previously reported in one case-control study (10) and two cohort studies (15, 16), but these studies included cigarette smokers. No association was reported in a third case-control study based on small numbers of subjects (17). Our results are similar to the only previous report of risk by type of smokeless tobacco, which suggested a positive association for chewing tobacco, but not for snuff (10).

Support for an association between pipe smoking and pancreatic cancer is weaker than that for cigar smoking and smokeless tobacco. Most studies have failed to find an association between pipe smoking and pancreatic cancer (12–14, 16, 18, 19), with only two studies reporting positive findings (10, 20).

Our estimates of pancreatic cancer risk associated with cigar smoking and use of smokeless tobacco were similar to those previously reported for cigarette smoking (5). The chemistry of cigar smoke is qualitatively similar to that of cigarettes, however, many quantitative differences do exist (2). Tobacco-specific *N*-nitrosamines (TSNA) are present in cigar smoke at significantly higher levels than in cigarette smoke. In particular, cigar smoke is richer than cigarette smoke in the highly carcinogenic TSNA N′-nitrosonorcotinine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The most important carcinogenic agents present in smokeless tobacco are TSNA, whereas the levels of polycyclic aromatic hydrocarbons in smokeless tobacco appear to be too low to make a significant contribution to smokeless tobacco carcinogenicity (2). Cigarette filters reduce the concentration of inhaled particulate containing the carcinogenic polycyclic aromatic hydrocarbons but do not significantly reduce the TSNA level. Switching from nonfilter cigarettes to filter cigarettes does not appear to lower the risk of pancreatic cancer (5, 10), suggesting that TSNA might play a more important role than polycyclic aromatic hydrocarbons in tobacco-induced pancreatic cancer. In addition, a recent study found measurable amounts of NNK and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in human pancreatic juice with significantly higher levels among smokers than nonsmokers (21). Although it is unclear to what extent nitrosamines might be activated in the human pancreas (22, 23), NNK and NNAL are metabolically activated in the liver (24) and excreted into the bile. NNK metabolites have been detected and measured in the bile of rats after *intra peritoneum* administration of NNK (25) and are known to induce pancreatic tumors in experimental studies (26).

Our study has a number of strengths, including analyses based solely on nonsmokers of cigarettes, its population-based study design, availability of information obtained from direct interviews with patients, and a review of diagnostic material for all pancreatic cancer cases. Some possible limitations are also apparent. First, most point estimates are not statistically significant. We believe, however, that the consistency of the patterns of risk (*e.g.*, higher risks among heavily exposed subjects), coupled with similar results from previous studies, suggests that the observed associations between heavy use of smokeless tobacco/cigar use and pancreatic cancer are unlikely to be due to chance. Second, because 40% of patients initially identified for study died before the interview could be conducted, survival

bias cannot be ruled out. A methodological substudy indicated that cigarette smoking habits of cases who survived enough to be interviewed were similar to those of cases who died before interview (5), suggesting that survival was not related to tobacco use and is unlikely to explain our findings.

In summary, our results suggest that heavy use of smokeless tobacco and possibly cigar smoking may increase the risk of pancreatic cancer among nonsmokers of cigarettes. Because of the recent rise of noncigarette tobacco use in the United States, coupled with the misconception that noncigarette tobacco is a safe product (2), additional research is needed to better understand whether smoking cigars and smokeless tobacco cause pancreatic cancer.

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