A Prospective Study of Cigarette Smoking and the Risk of Pancreatic Cancer

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Objectives: To prospectively examine the excess incidence of pancreatic cancer among cigarette smokers and to examine the influence of smoking cessation on the risk of pancreatic cancer.

Methods: We obtained data on cigarette smoking and other risk factors for pancreatic cancer from 118 339 women aged 30 to 55 years and 49 428 men aged 40 to 75 years who were without diagnosed cancer. During the 2 116 229 persons-years of follow-up, pancreatic cancer was diagnosed in 186 participants.

Results: The multivariate relative risk of pancreatic cancer for current smokers was 2.5 (95% confidence interval, 1.7-3.6). A significant, positive trend in risk with increasing pack-years of smoking was observed (P for trend=.004), although this association was confined to cigarette consumption within the past 15 years. Compared with participants who continued to smoke, former smokers had a 48% reduction in pancreatic cancer risk within 2 years of quitting. Ultimately, the relative risk of pancreatic cancer among former smokers approached that for never smokers after less than 10 years of smoking cessation. Overall, the proportion of pancreatic cancers attributable to cigarette smoking was 25%.

Conclusions: Cigarette smoking is associated with an increased risk of pancreatic cancer. The rapid reduction in risk associated with quitting suggests that smoking cessation could eliminate 25% of the 27 000 deaths from pancreatic cancer occurring annually in the United States.

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CANCER OF the pancreas represents the fifth leading cause of cancer-related mortality in the United States.[1] Nonetheless, relatively few risk factors are known for this malignancy.[2] Retrospective studies have suggested that a history of cigarette smoking elevates a person's lifetime risk of pancreatic cancer 1.9-fold to 5.5-fold.[2-17] However, the strength of this association remains uncertain because of the retrospective design of these analyses and their failure to consistently demonstrate a dose-response relationship. In addition, because pancreatic cancer is a rapidly fatal malignancy, these studies often rely on proxy, next-of-kin respondents to elicit smoking history, which may have further obscured the relationship.

Prospective studies can overcome these limitations. However, fewer prospective analyses of pancreatic cancer epidemiology have been conducted and these studies[18-23] have been limited by small numbers of cases. We therefore used data from 2 large prospective cohort studies[24,25] to quantify the excess incidence of pancreatic cancer among cigarette smokers and to ascertain the proportion of pancreatic cancers attributable to smoking. Furthermore, we sought to examine the relationship between time since quitting smoking and reductions in the relative risk (RR) of pancreatic cancer.

RESULTS

At the initiation of the Nurses' Health Study in 1976, 33.2% of the women were current smokers, 23.5% were past smokers, and 43.3% never smoked. At the start of the Health Professionals Follow-up Study in 1986, 9.6% of the men were current smokers, 41.8% were past smokers, and 48.6% never smoked. For both cohorts, smoking status was updated biennially. Consequently, by 1990, the correspond-

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SUBJECTS AND METHODS

STUDY COHORTS

We analyzed data from 2 ongoing cohorts, the Nurses' Health Study[24] and the Health Professionals Follow-up Study.[25] The Nurses' Health Study began in 1976 when 121 700 American female registered nurses aged 30 to 55 years completed a mailed questionnaire on known or suspected risk factors for cancer and coronary heart disease. In 1980, the questionnaire was expanded to include an assessment of diet. The Health Professionals Follow-up Study began in 1986 when 51 529 American male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians aged 40 to 75 years completed a mailed questionnaire on known or suspected risk factors for cancer and coronary heart disease, which also included an assessment of diet. Every 2 years, participants in these cohorts have been sent follow-up questionnaires to update information on potential risk factors and to identify newly diagnosed cases of cancer and other diseases.

EXPOSURE DATA

On the 1976 Nurses' Health Study questionnaire[24] and the 1986 Health Professionals Follow-up Study questionnaire,[25] past and current smokers were asked to indicate the average number of cigarettes they smoked per day, the age at which they began smoking, and, among past smokers, the age at which they stopped smoking. Information on smoking status and the number of cigarettes smoked has been updated biennially. On each questionnaire, current smokers were further classified as smoking: 1 to 4, 5 to 14, 15 to 24, 25 to 34, 35 to 44, or 45 or more cigarettes per day. To examine the influence of packs per day among current smokers, categories of current smoking were collapsed into 1 to 14, 15 to 24, and 25 or more cigarettes per day. These categories were created before data analysis. Study participants also provided information on age, height, weight, and history of diabetes mellitus.

Alcohol consumption may potentially confound the association between cigarette smoking and pancreatic cancer because smokers tend to drink more, and alcohol intake may be associated with an increased risk of pancreatic cancer. Consumption of fruits and vegetables may also confound the association between smoking and pancreatic cancer. The 1980 Nurses' Health Study questionnaire and the 1986 Health Professionals Follow-up Study questionnaire included a semiquantitative food-frequency questionnaire to assess diet as well as the average frequency of alcohol intake. In the present analysis, levels of alcohol intake were categorized into abstinence, or 0.1 to 1.5, 1.6 to 5.0, 5.1 to 15.0, 15.1 to 25.0, or more than 25 g/d. Servings of fruits and vegetables were categorized into energy-adjusted quintiles. The reproducibility and validity of the self-reported dietary intakes have been documented previously.[26-30]

POPULATION FOR ANALYSIS

We excluded from the analysis all participants who reported a history of cancer (other than nonmelanoma skin cancer) at baseline. This left 118 339 women and 49 428 men eligible for follow-up. To examine the possible confounding effects of alcohol and other dietary consumption, we analyzed data from 1980 to 1992 and excluded participants who did not complete the food-frequency questionnaire as well as those with a history of cancer at

ing rates among the women were 19.4% current, 37.4% former, and 43.2% never smokers; rates among the men were 7.9% current, 43.6% former, and 48.5% never smokers. During the 2 116 229 person-years of follow-up, pancreatic cancer was diagnosed in 126 women and 60 men. Of these 186 individuals, 181 (97%) died of the disease.

Participants in the Nurses' Health Study and the Health Professionals Follow-up Study who currently smoked cigarettes experienced substantially higher rates of pancreatic cancer compared with never smokers (**Table 1**). In contrast, former smokers did not experience a significant elevation in risk. Although the RR associated with current smoking was less for women than for men, this difference was readily compatible with random variation ($P=.73$). Furthermore, the RRs of pancreatic cancer among current smokers did not change appreciably by multivariate adjustment for the effects of body mass index and a history of diabetes mellitus (multivariate RR for the cohorts combined, 2.5 [95% CI, 1.7-3.6]).

For women and men combined, the RR of pancreatic cancer associated with ever smoking was 1.6 (95% CI, 1.1-2.2). Based on this risk estimate, 25% of pancreatic cancers were attributable to past or present cigarette smoking.

Among current smokers, we failed to observe a clear relationship between the number of cigarettes smoked per day and the risk of pancreatic cancer. The multivariate RRs of pancreatic cancer were 2.0 (95% CI, 1.2-3.6) for participants who smoked less than 15 cigarettes per day, 3.2 (95% CI, 2.1-4.9) for those who smoked 15 to 24 cigarettes per day, and 2.0 (95% CI, 1.2-3.6) for those who smoked 25 cigarettes or more per day.

To further assess the dose-response relationship, we examined the association between cumulative cigarette exposure measured in pack-years and the risk of pancreatic cancer. Since age is strongly correlated with duration of smoking, we adjusted for age using 2-year categories to reduce residual confounding in this analysis. For both women and men, we observed a statistically significant linear trend between total pack-years of smoking and the risk of pancreatic cancer (P for trend=.004) (**Table 2**). For the women and men combined, there was no apparent increase in risk for participants who consumed less than 10 pack-years of cigarettes, whereas the RR for participants who consumed 26 to 50 pack-years was 1.9 (95% CI, 1.3-2.8). Notably, we observed no additional risk associated with smoking for more than 26 to 50 pack-years.

We also examined the relationship between time

the time of the dietary assessment, leaving 89 516 women and 47 950 men eligible for that analysis.

IDENTIFICATION OF PANCREATIC CANCER CASES

On each questionnaire we inquired whether a diagnosis of pancreatic cancer was made and, if so, the date of the diagnosis. For this analysis, the follow-up rate was 96% of total possible person-years for the Nurses' Health Study and 94% for the Health Professionals Follow-up Study. Most of the deaths in these cohorts were reported by family members or the postal system in response to the follow-up questionnaires. In addition, we used the National Death Index,[31] a highly sensitive method of identifying deaths among nonrespondents. All participants who reported pancreatic cancer (or the next of kin for decedents) were contacted for permission to review the relevant hospital records and confirm the reported diagnosis. Medical records or death certificates were obtained from 99% and 98% of the cases among the Nurses' Health Study and Health Professionals Follow-up Study cohorts, respectively. All records were reviewed by physicians who were blinded to exposure status. We based our analysis on all incident pancreatic cancers because the rate of accuracy of self-reporting was high (99% and 98% for the Nurses' Health Study and Health Professionals Follow-up Study cohorts, respectively). In this analysis, we included 126 cases of pancreatic cancer among the women and 60 cases among the men.

STATISTICAL ANALYSIS

The primary analysis used incidence rates with person-years of follow-up in the denominator. For each participant, person-years of follow-up were counted from the date of return of the baseline questionnaire (1976 in the cohort of women and 1986 in the cohort of men) to May 31, 1992, for the women or January 31, 1992, for the men. For the participants in both cohorts for whom a diagnosis of pancreatic cancer was made or who died of another cause, person-years of follow-up were calculated according to the most recently completed questionnaire, but the period of follow-up terminated with the diagnosis of pancreatic cancer or death. If no questionnaire was returned for a follow-up cycle, the most recently recorded data were used for the subsequent follow-up interval. For exposures (dietary intake and body mass index) that were not updated, the initial value was carried throughout the follow-up period.

We used RR as a measure of association defined as the incidence of pancreatic cancer among the participants in each exposure category divided by the corresponding rate in the reference category. Age-adjusted RRs and 95% confidence intervals (CIs) were calculated after stratification according to 5-year categories. We used proportional hazards models to adjust for other potential risk factors for pancreatic cancer.[32] When appropriate, we used the Mantel-Extension test for linear trend across categories of exposures and reported the 2-tailed P values.[33] We conducted additional stratified analyses to assess effect modification between exposures. Tests for the homogeneity of risk estimates across strata were based on a weighted sum of the squared deviations of the stratum-specific log-odds ratios from their weighted mean.[34]

The proportion of all cases of pancreatic cancer in each cohort that was attributable to smoking was calculated as the proportion of cases among former or current smokers that was attributable to ever smoking ($[RR-1] \div RR$) multiplied by the prevalence of former or current smoking among the participants with pancreatic cancer.[34]

since quitting smoking and the risk of pancreatic cancer. Compared with current smokers, the RR among former smokers diminished precipitously and approached the RR for never smokers within 10 years following cessation (**Figure**). Among former smokers who had discontinued smoking within the past 2 years, the RR of pancreatic cancer was reduced by 48% compared with current smokers. This pattern of decline was observed despite adjusting for other risk factors for pancreatic cancer, including total pack-years of cigarette smoking.

To further ascertain whether the difference in RR between current and former smokers simply reflected disparities in levels of consumption, we reassessed the influence of pack-years among either current or former smokers (**Table 3**). For each category of pack-years, the RR was greater for current smokers than for former smokers. Moreover, we observed a significant linear trend between pack-years of smoking and the risk of pancreatic cancer among current smokers (P for trend $<.001$), whereas we failed to detect a significant trend among former smokers (P for trend $=.30$). Nonetheless, current smokers experienced little additional risk beyond 16 to 25 pack-years of consumption.

Because the relationship between pack-years and pancreatic cancer risk appeared to plateau with increasing duration of exposure, we examined among current smokers the differential effects of cigarette consumption within the past 15 years or consumption beyond that time. Since we observed a significant linear trend between pack-years of smoking and pancreatic cancer risk only among current smokers, we excluded person-years assigned to former smokers from this analysis. In the proportional hazards model, we included values for pack-years of smoking within each period simultaneously (**Table 4**). When restricted to cigarette consumption less than 15 years in the past, the RR of pancreatic cancer increased monotonically with increasing pack-years of smoking (P for trend $=.01$). However, for consumption of 15 or more years in the past, we did not observe an association between pack-years and pancreatic cancer risk (P for trend$=.48$).

Finally, to assess the possible confounding effects of alcohol intake as well as fruit and vegetable consumption on the relationship between smoking and pancreatic cancer, we analyzed data from 1980 to 1992 among participants who provided dietary information. Although the analysis was limited to 149 cases, the association between smoking and pancreatic cancer was unchanged. Adjusting for alcohol intake and fruit and

vegetable consumption, the RR for pancreatic cancer among former smokers was 1.2 (95% CI, 0.8-1.8), whereas the RR among current smokers was 2.8 (95% CI, 1.9-4.3). Moreover, after adjusting for these dietary factors, the RR was 2.0 (95% CI, 1.3-3.0) for ever smokers who consumed 26 to 50 pack-years and 2.4 (95% CI, 1.4-4.1) for those who smoked more than 50 pack-years (P for linear trend <.001).

COMMENT

In this prospective analysis, we found a consistent, independent positive association between cigarette smoking and the risk of pancreatic cancer. The RR of pancreatic cancer, approximately 2.5-fold among current smokers, was similar in 2 independently conducted cohort studies[24,25] and was similar among women and men. In contrast, we observed little or no elevation in risk among former smokers. Within the combined cohorts, 25% of all cases of pancreatic cancer were attributable to cigarette smoking.

Using predominantly retrospective data, previous studies[2-5,7,8,10-14,16,17] observed a 2-fold to 3-fold increase in risk of pancreatic cancer among current smokers and a minimal, if any, excess risk among former smokers. However, the dose-response relationship between smoking and pancreatic cancer was either weak or absent in the majority of these analyses. We observed a significant increase in the risk of pancreatic cancer with increasing pack-years of smoking among both ever and current smokers, although there appeared to be little additional risk beyond 16 to 25 pack-years of cigarette consumption. Such a finding would suggest either that smoking is not causally related to pancreatic cancer or that smoking exerts its effect predominantly in the later stages of carcinogenesis. In support of the latter hypothesis, we observed a significant dose-response relationship among current smokers when we restricted our analysis to cigarette smoking within the past 15 years, whereas there was no effect of consumption 15 or more years in the past. Consistent with our findings, Howe et al[12] recently observed in a large case-control study that the dose-response relationship was much stronger when the analysis was confined to consumption within the past 15 years.

At least 4 case-control studies[5,8,12,13] observed that the risk of pancreatic cancer among former smokers approached the risk for never smokers within a decade following smoking cessation. In the present analysis, we observed that the excess risk among former smokers essentially disappeared after less than 10 years of smoking cessation. This relationship of time since quitting to decline in risk was independent of pack-years of consumption or the presence of other risk factors.

The prospective nature of our study precluded recall bias and the need for next-of-kin respondents,

Table 1. Relative Risk (RR) of Pancreatic Cancer According to Smoking History*

Population	Never Smokers	Former Smokers	Current Smokers
Total			
No. of cases	62	63	61
Person-years	931 091	660 267	524 871
Adjusted RR† (95% CI)	1.0	1.2 (0.8-1.7)	2.4 (1.7-3.4)
Multivariate RR‡ (95% CI)	1.0	1.2 (0.8-1.7)	2.5 (1.7-3.6)
Women			
No. of cases	42	34	50
Person-years	799 891	545 078	501 015
Age-adjusted RR (95% CI)	1.0	1.1 (0.7-1.7)	2.2 (1.5-3.3)
Multivariate RR‡ (95% CI)	1.0	1.1 (0.7-1.7)	2.4 (1.6-3.6)
Men			
No. of cases	20	29	11
Person-years	131 200	115 189	23 856
Age-adjusted RR (95% CI)	1.0	1.3 (0.7-2.3)	3.1 (1.5-6.2)
Multivariate RR‡ (95% CI)	1.0	1.3 (0.7-2.3)	3.0 (1.5-6.3)

*CI indicates confidence interval.
†Adjusted for age in 5-year intervals and gender.
‡Multivariate RR adjusted for age in 5-year intervals, gender, body mass index, and history of diabetes mellitus.

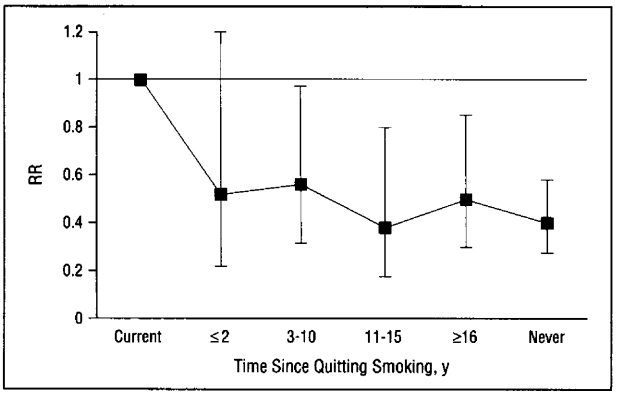
Table 2. Relative Risk (RR) of Pancreatic Cancer According to Pack-Years of Smoking*

Population	Pack-Years of Smoking: Never	1-10	11-25	26-50	>50	P for Trend
Total						
No. of cases	62	18	34	50	22	
Person-years	931 091	351 017	380 164	349 833	104 124	.004
Multivariate RR† (95% CI)	1.0	1.0 (0.6-1.6)	1.5 (1.0-2.3)	1.9 (1.3-2.8)	1.8 (1.1-3.0)	
Women						
No. of cases	42	14	22	38	10	
Person-years	799 891	320 999	326 785	310 923	87 386	.01
Multivariate RR (95% CI)	1.0	1.1 (0.6-1.9)	1.6 (1.0-2.7)	2.1 (1.4-3.3)	1.3 (0.7-2.7)	
Men						
No. of cases	20	4	12	12	12	
Person-years	131 200	30 018	53 379	38 910	16 738	.004
Multivariate RR† (95% CI)	1.0	0.9 (0.3-2.6)	1.3 (0.7-2.7)	1.5 (0.7-3.1)	2.8 (1.3-5.7)	

*CI indicates confidence interval.
†Multivariate RR adjusted for age in 2-year intervals, gender, body mass index, and history of diabetes mellitus.

potential sources of distortion in retrospective studies of pancreatic cancer epidemiology. Moreover, because exposure data were collected before the diagnosis of any cases of pancreatic cancer, any error in recall would have attenuated rather than exaggerated a true association. To avoid any misclassification of exposure during longitudinal follow-up, measurements of cigarette consumption were updated biennially.

Differential follow-up is unlikely to have made a material contribution to these findings, since we estimate that we accurately identified more than 98% of the deaths in these cohorts.[31] Furthermore, it is unlikely that smoking was acting as a surrogate for other predictors of pancreatic cancer, since the risk estimates associated with past or present smoking did not change materially after adjustment for other known or suspected risk factors for pancreatic cancer.



Multivariate relative risks (RRs) of pancreatic cancer in relationship to time since stopping smoking. Current smokers were the reference category. Error bars represent 95% confidence intervals. The 95% confidence intervals and RRs were adjusted for age in 2-year intervals, gender, body mass index, history of diabetes mellitus, and pack-years of smoking. Horizontal line identifies an RR of 1.0.

One potential limitation of the present study is that the data set was confined to a predominantly white population. Although our findings may not be generalizable to other ethnic groups, Silverman and colleagues[14] recently found that the relationship between smoking and pancreatic cancer was virtually identical across racial subgroups.

The mechanisms by which cigarette smoking influences pancreatic cancer risk has not been established. Pancreatic tumors can be induced experimentally in animals by administration of tobacco-specific nitrosamines in drinking water, as well as by parenteral administration of other *N*-nitroso compounds.[35,36] Furthermore, autopsy studies demonstrate substantial pancreatic tissue damage among smokers compared with nonsmokers.[37] It has been suggested that tobacco-specific carcinogens reach the pancreas either through the blood or through refluxed bile that is in contact with the pancreatic duct.[15] Our findings suggest that smoking may act late in the carcinogenic pathway. Further investigation will be needed to clarify the mechanisms by which smoking contributes to pancreatic tumorigenesis.

Table 3. Relative Risk (RR) of Pancreatic Cancer According to Pack-Years of Smoking for Current and Former Smokers*

Population	Pack-Years of Smoking: Never	1-10	11-25	26-50	>50	*P* for Trend
Current smokers						
No. of cases	62	2	12	32	15	
Pearson-years	931 091	57 867	161 124	230 093	75 787	<.001
Multivariate RR† (95% CI)	1.0	1.3 (0.3-5.4)	2.7 (1.4-5.1)	2.8 (1.8-4.4)	2.1 (1.2-3.8)	
Former smokers						
No. of cases	62	16	22	18	7	
Person-years	931 091	293 150	219 040	119 740	28 337	.30
Multivariate RR† (95% CI)	1.0	1.0 (0.6-1.7)	1.2 (0.7-2.0)	1.2 (0.7-2.1)	1.3 (0.6-2.9)	

**CI indicates confidence interval.*
†Multivariate RR adjusted for age in 2-year intervals, gender, body mass index, and history of diabetes mellitus.

Table 4. Relative Risk (RR) of Pancreatic Cancer According to Pack-Years of Smoking and Period of Cigarette Consumption*

Period of Exposure	Pack-Years of Smoking: 0	1-5	6-15	16-25	>25	*P* for Trend
Cigarette consumption <15 y in the past						
No. of cases	62	1	34	18	8	
Person-years	931 091	37 202	296 650	137 750	53 269	.01
Multivariate RR† (95% CI)	1.0	0.6 (0.5-6.5)	3.9 (0.9-16)	4.8 (1.1-22)	5.5 (1.1-27)	
Cigarette consumption ≥15 y in the past						
No. of cases	64	4	9	21	25	
Person-years	974 379	84 181	173 131	123 114	101 157	.69
Multivariate RR† (95% CI)	1.0	1.6 (0.3-8.1)	0.5 (0.1-2.3)	0.8 (0.2-3.3)	0.5 (0.1-2.2)	

**Analysis restricted to person-years assigned to current smokers and never smokers only. Smoking status was updated biennially. CI indicates confidence interval.*
†Multivariate RR adjusted for age in 2-year intervals, gender, body mass index, history of diabetes mellitus, and pack-years of smoking in the other period.

In conclusion, our findings suggest a causal relationship between cigarette smoking and pancreatic cancer, particularly among current smokers. The rapid reduction in risk associated with quitting suggests that smoking cessation could eliminate 25% of the 27 000 deaths from pancreatic cancer occurring annually in the United States.

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