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Research Article

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Active and Passive Smoking and the Risk of Pancreatic Cancer in the Netherlands Cohort Study

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Abstract

Background: To date, cigarette smoking is the most consistent risk factor for pancreatic cancer. We prospectively examined the role of active cigarette smoking, smoking cessation, and passive smoking as determinants for pancreatic cancer.

Methods: The Netherlands Cohort Study consisted of 120,852 men and women who completed a baseline questionnaire in 1986. After 16.3 years of follow-up, 520 incident pancreatic cancer cases were available for analysis. A case-cohort approach was employed using the person-years of follow-up of a random subcohort (n = 5,000), which was chosen immediately after baseline.

Results: Compared with never cigarette smokers, both former and current cigarette smokers had an increased pancreatic cancer risk [multivariable-adjusted hazard rate ratio (HR), 1.34; 95% confidence interval (CI), 1.02-1.75 and HR, 1.82; 95% CI, 1.40-2.38, respectively]. We observed an increased pancreatic cancer risk per increment of 10 years of smoking (HR, 1.15; 95% CI, 1.08-1.22) and an HR of 1.08 per increment of 10 cigarettes/d (95% CI, 0.98-1.19). Quitting smoking gradually reduced pancreatic cancer risk and approached unity after ≥20 years of quitting. No association was observed for passive smoking exposure and pancreatic cancer risk in women; in men, this association was not investigated because >90% of the men were ever smokers.

Conclusions: Overall, our findings confirmed that cigarette smoking is an important risk factor for pancreatic cancer, whereas quitting smoking reduced risk. No association was observed between passive smoking exposure and pancreatic cancer risk in women.

Impact: Quitting smoking would benefit the burden on pancreatic cancer incidence. *Cancer Epidemiol Biomarkers Prev; 19(6); 1612–22. ©2010 AACR.*

Introduction

To date, cigarette smoking is the most consistent risk factor for pancreatic cancer (1). Most studies, including several cohort studies, a meta-analysis, and a pooled analysis of eight cohorts, indicated that current smokers had about a 2-fold increased pancreatic cancer risk compared with never smokers (2-6). Former smokers experience lower increased risks of pancreatic cancer as compared with current smokers, with risks ranging from 1.1 to 1.6 (2, 7-11). Pancreatic cancer risk increases with both number of cigarettes smoked daily (3, 5-8, 12) and duration of smoking (3, 5, 8, 10, 11). After quitting cigarette smoking, the risk decreases gradually within 10 to 15 years towards unity (5, 8, 12, 13).

Data on the effect of passive smoking on pancreatic cancer risk is scarce because studies have been hindered by the relatively few nonsmokers of any type of tobacco. Exclusion of tobacco smokers from such studies is important to estimate the independent effect of passive smoking. Thus far, four case-control (14-17) and four cohort studies (7, 9, 18, 19) have examined the relationship between passive smoking exposure and the risk of pancreatic cancer. Three of these studies observed a positive association with passive smoking in never smokers (7, 15, 18).

In the current study, we examined active cigarette smoking, smoking cessation, and passive smoking as determinants for pancreatic cancer in a large prospective cohort study in the Netherlands.

Materials and Methods

Study population and cancer follow-up

The study design of the Netherlands Cohort Study has been reported in detail elsewhere (20). Briefly, the Netherlands Cohort Study was begun in September 1986 and included initially 58,279 men and 62,573 women ages 55 to 69 years from 204 Dutch municipalities with computerized population registries. A self-administered food frequency and lifestyle questionnaire was completed at

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baseline. For increased efficiency in the processing of the questionnaire and follow-up, the case-cohort approach was used (21). Incident cases were derived from the entire cohort, whereas the person-years at risk were estimated from a random sample of 5,000 subjects (2,411 men and 2,589 women). This subcohort was chosen immediately after baseline and followed up for vital status information. The entire cohort is being monitored for cancer occurrence by annual record linkage to the Netherlands Cancer Registry and the Netherlands Pathology Registry (22, 23). A total of 16.3 years of follow-up (baseline to December 2002) was used for the current analysis. Only one subcohort member was lost to follow-up and completeness of follow-up was estimated to be >96% (24).

All prevalent cancer cases at baseline other than skin cancer were excluded, resulting in a subcohort of 4,774 men and women. Of the 567 incident pancreatic cancer cases (International Classification of Diseases for Oncology-3 code C25), cases with endocrine subtypes (International Classification of Diseases for Oncology-3 code C25.4; $n = 1$) were excluded. Sixty-two percent of the 566 pancreatic cancer cases were microscopically confirmed pancreatic cancer ($n = 350$), whereas confirmation was lacking for 38% (nonmicroscopically confirmed pancreatic cancer; $n = 216$). Diagnosis of the latter group was made by the treating clinician and was based on clinical symptoms, physical examination, and imaging results. Data were abstracted and recorded by a trained tumor registrar (25). The Netherlands Cohort Study has been approved by the institutional review boards of the TNO Nutrition and Food Research Institute (Zeist, the Netherlands) and Maastricht University (Maastricht, the Netherlands).

Exposure assessment

In the questionnaire, tobacco smoking was addressed through questions on smoking status (never, former, or current smoker) and inhalation for cigarette, cigar, and pipe smokers (26, 27). In addition, open-ended questions were asked on the ages at first and last exposure to smoking, smoking frequency, and smoking duration for cigarette, cigar, and pipe smokers. Furthermore, questions were asked about the cigarette brand most commonly smoked with or without filter-tip and the proportion of a cigarette actually smoked (using a visual analog scale; ref. 27). Using cigarette brand–specific information obtained from the Dutch Inspectorate for Health Protection, the Dutch Foundation on Smoking and Health, and the Dutch Foundation of the Tobacco Industry in combination with daily cigarette smoking frequency and the proportion of a cigarette actually smoked, we calculated the daily exposure to tar and nicotine for ever cigarette smokers (27). Passive smoking exposure was investigated using questions on smoking habits of parents and spouses, exposure to passive smoking at work (past or present), and duration of current daily exposure to passive smoking (open-ended question; private and occupational settings combined; ref. 27). The dietary section of the questionnaire was a 150-item semiquantitative food-frequency questionnaire. Questionnaire data were key-entered and processed for all incident cases in the cohort and subcohort members in a standardized manner, blinded with respect to case/subcohort status. This was done to minimize observer bias in the coding and interpretation of the data. Subcohort members and cases with incomplete or inconsistent dietary data were excluded from analyses. These subjects had either (*a*) left >60 (of the 150 items) questionnaire items blank and ate <35 items at least once a month or (*b*) left one or more item blocks (groups of items, e.g., beverages) blank. Additional details are given elsewhere (28). This resulted in a final subcohort of 4,438 subjects (2,191 men and 2,247 women) and 520 exocrine pancreatic cancer cases (280 men and 240 women) available for analysis.

Statistical analysis

Age-adjusted and multivariable-adjusted hazard rate ratios (HR) and corresponding 95% confidence intervals (95% CI) were estimated using Cox proportional hazards models. The total person-years at risk estimated from the subcohort were used in the analyses (29). Standard errors were estimated using a robust covariance matrix estimator to account for increased variance due to sampling from the cohort (30). We tested the proportional hazards assumption using the scaled Schoenfeld residuals (31). Interactions on a multiplicative scale between sex and any of the smoking variables used in the current study were tested for pancreatic cancer and never found to be statistically significant ($P_{interaction} > 0.05$). Therefore, results for analyses on cigarette smoking are presented for both sexes combined. No analyses were done on cigar and pipe smoking because among never cigarette smokers, only three cases ever smoked cigars or pipes. For passive smoking exposure, analyses were restricted to women (124 cases, 1,312 subcohort members) who never smoked cigarettes, cigars, or pipes. We excluded men in these analyses because >90% of the men were ever smokers.

Based on questionnaire data, the following categorical variables were constructed for active cigarette smoking: status (former smoker/current smoker), frequency (0.1 to <10, 10 to <20, ≥20 cigarettes/d), inhalation (no/yes), filter usage (filter-tipped/non–filter-tipped), duration (0.1 to <20, 20 to <40, ≥40 years), time since cessation (quit ≥20, 15 to <20, 10 to <15, 0.1 to <10 years, or current smoker), and tar (0.1 to <200, 200 to <400, ≥400 mg/d) and nicotine exposure (0.1 to <10, 10 to <20, 20 to <30, ≥30 mg/d). HRs for pancreatic cancer were estimated accordingly, with subjects who never smoked cigarettes regarded as the reference group. HRs were also estimated for continuous exposures using an increment of 10 cigarettes per day for frequency. For duration and years since cessation, an increment of 10 years was used. For tar and nicotine exposure, we used an increment of 100 mg and 10 mg/d, respectively. Passive smoking exposure was operationalized in four separate variables: spouse smoking status (never smoked/former smokers/current smokers), parental smoking (no/yes), exposure to passive smoking at work (never exposed/occasionally exposed/regularly or always exposed), and duration of passive smoking exposure

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(categorical variable: never, 0.1 to <3, ≥3 h/d; continuous variable: increments of 1 h/d).

Based on the literature, the following variables were considered as potential confounders: age, sex, body mass index (BMI), energy intake, alcohol intake, intake of vegetables and fruit, level of education, moderate nonoccupational physical activity, family history of pancreatic cancer, history of diabetes mellitus, and hypertension. These potential confounding variables were added to the multivariable-adjusted model if they (*a*) were associated with the disease and with the exposure of interest and (*b*) changed the risk estimate by at least 10% (using a backwards stepwise procedure). For analyses on cigarette smoking, the following confounders were included in the first multivariable-adjusted model: age at baseline (y), sex, BMI (kg/m^2), alcohol intake (g/d), and intake of fruit (g/d). For analyses on passive smoking, the following confounders were included in the multivariable-adjusted model: age at baseline (y), BMI (kg/m^2), and level of education (primary school or lower vocational school/intermediate vocational school or high school/higher vocational school or college). In additional analyses on cigarette smoking, we included smoking status, duration, and frequency simultaneously into the model to identify which factor of smoking in this model is most important to pancreatic cancer risk. In additional analyses on the categorical variable of time since cessation, frequency and duration were included in the model. For the continuous variable of time since cessation, frequency, duration, and current smoking status (yes/no) were additionally included in the model. Furthermore, we investigated whether inhalation and filter usage had any effect on top of duration, frequency, and current smoking status. We also investigated this for tar and nicotine exposure; however, we did not include frequency in these models because the variables of tar and nicotine exposure were calculated by multiplying the number of cigarettes per day by the amount of tar and nicotine per cigarette. In additional analyses, we excluded cigar or pipe smokers. To enable comparison, age- and sex-adjusted analyses were restricted to subjects included in multivariable-adjusted analyses. For each analysis, trends were evaluated with the Wald test by assigning participants the median value for each level of the categorical exposure variable among the subcohort members and this variable was entered as a continuous term in the Cox regression model. For the trend analysis on cigarette smoking variables, never cigarette smokers were excluded to evaluate whether a large amount of exposure was measurably worse than a small amount of exposure.

In the present study, the overall analyses included all pancreatic cancer cases. We restricted additional analyses to microscopically confirmed pancreatic cancer cases to create a group with a higher degree of diagnostic certainty of pancreatic cancer, which was shown to be important in previous studies (32, 33). In additional analyses, individuals who reported a history of diabetes at baseline (n = 185) were excluded. To evaluate whether early symptoms of disease before diagnosis could have influenced the results, early cases (diagnosed within 2 years after baseline) were excluded in additional analyses.

In addition, we calculated the population-attributable fraction (PAF) of pancreatic cancer cases to estimate how many cases theoretically could be prevented if no individuals would smoke. The PAF was calculated according to the following equation: PAF = P_d×[(RR-1) / RR] (refs. 34, 35). P_d is the proportion of smokers among all pancreatic cancer cases, and RR is the adjusted risk estimate of pancreatic cancer risk comparing ever versus never smokers. The confidence limits were estimated using: ln(1-PAF) (ref. 34). All analyses were done using the STATA statistical software package (Intercooled STATA, version 9). All P values were based on two-sided tests and considered statistically significant if $P < 0.05$.

Results

In Table 1, baseline characteristics (stratified by sex) are presented. Most characteristics did not differ between pancreatic cancer cases and subcohort members; however, there were more current smokers among cases than among subcohort members, especially in men.

Compared with never cigarette smokers, both former and current cigarette smokers had an increased pancreatic cancer risk (age-adjusted HR, 1.37; 95% CI, 1.05-1.78 and HR, 1.88; 95% CI, 1.44-2.44, respectively; Table 2). We observed an increased pancreatic cancer risk of 51% (95% CI, 1.12-2.04) with smoking ≥20 cigarettes/d compared with never cigarette smoking (Table 2), but no clear dose-response relation was present (P_{trend} = 0.96). Smokers smoking one package per day (i.e., 20 cigarettes/d) had a similar risk, showing an increased risk of 49% (95% CI, 1.05-2.12; data not shown). Most pancreatic cancer cases smoked <40 cigarettes/d; only 15 cases smoked ≥40 cigarettes. For duration of smoking, we observed a significantly increased pancreatic cancer risk per increment of 10 years (age-adjusted HR, 1.15; 95% CI, 1.08-1.22; Table 2), with a clear dose-response effect observing a 2-fold increased cancer risk comparing ≥40 years of smoking to never cigarette smoking. Quitting smoking gradually reduced the risk of pancreatic cancer and approached unity after ≥20 years of quitting smoking (Table 2).

Our findings remained after the inclusion of the confounding variables in the multivariable model (Table 2). However, results were modified when smoking variables were included simultaneously into the model. The increased risk estimates observed for current smoking status, frequency, and years of cessation diminished and became nonsignificant after including other aspects of smoking in the model (data not shown). However, additional adjustment for other smoking aspects had little influence on the risk estimates of years of smoking cigarettes, showing just slightly attenuated HRs compared with the age- and sex-adjusted and the multivariable-adjusted HRs (data not shown).

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It made little difference whether subjects did or did not inhale cigarette smoke; we observed in both situations a significantly increased pancreatic cancer risk after adjustment for age and sex (Table 3). In addition, both filter-tipped and non–filter-tipped cigarettes significantly increased pancreatic cancer risk. Exposure to tar and nicotine significantly increased pancreatic cancer risk, but did not show dose-dependent relations (P_{trend} > 0.05). After inclusion of the confounding variables and the smoking variables duration, current smoking status, and frequency (frequency was only included in the models on inhalation and filter usage), the increased pancreatic cancer risks disappeared (Table 3).

When the association between the abovementioned cigarette smoking variables and pancreatic cancer risk were examined for men and women separately (data not shown), the risk estimates seemed to be stronger in men than in women. However, only 7% (n = 19) of the male cases never smoked cigarettes. Excluding nonmicroscopically confirmed pancreatic cancer cases did not change the risk estimates appreciably (data not shown). Also, risk estimates were not affected when excluding current cigar or pipe smokers (43 cases, 342 subcohort members) except for former smokers who still showed an increased but nonsignificant pancreatic cancer risk (multivariable-adjusted HR, 1.25; 95% CI, 0.94-1.66). The PAF of pancreatic cancer due to ever smoking for men and women combined was estimated as 27% (95% CI, 15-37), using a HR which was adjusted for age, sex, fruit intake, BMI, and alcohol intake (HR, 1.58; 95% CI, 1.25-2.01). Stratified by sex, the PAF of pancreatic cancer due to ever smoking was estimated as 46% (95% CI, 17-65) for men and as 16% (95% CI, 5-27) for women.

Regarding passive smoking in women, after adjusting for age, we observed no association between pancreatic cancer risk and smoking status from the spouse, parental smoking, being exposed at work to passive smoking (past or present), or duration of current passive smoking exposure (both in occupational and private setting; Table 4). Results were similar when including confounders into the model (Table 4) or when restricting the analyses to microscopically verified cases (data not shown). Our findings remained the same after excluding individuals who reported a history of diabetes at baseline from the analyses or after excluding the first 2 years of follow-up (data not shown).

Discussion

In the current analysis, we observed an 80% increased risk of pancreatic cancer for current smokers compared with never cigarette smokers, which is in agreement with other studies (3-5, 7-11, 36). In addition, we observed an increased pancreatic cancer risk for former smokers compared with never smokers and for incremental increases in number of years smoked, as found in previous research (8, 10, 11, 37). For cigarettes smoked per day, we observed an increased risk as well; however, the magnitude was less strong than in other cohort studies observing 2- to 3-fold increased risks for ≥20 cigarettes/d (5, 7-9, 12). Based on the current study, 27% of pancreatic cancer cases could hypothetically be prevented if people would not smoke. Similar estimates were found in previous studies (24% in ref. 37; 25% in ref. 12; and 27% in ref. 10). A few studies, however, found lower PAF values (15% in ref. 5 and 7% in ref. 38). This might be due to the fact that the PAF is very dependent on the prevalence of smoking in a population. This was also shown when we estimated the PAF separately for men and women, observing a PAF of 46% for men (93% ever smokers among male cases) and of 16% for women (50% ever smokers among female cases).

After ≥20 years of quitting smoking, pancreatic cancer risk approached the risk of never smokers. This was observed by one previous cohort as well (8), whereas other studies observed risk estimates similar to never smokers after 5 to 10 years (7, 12, 13, 36). A pooled cohort analysis observed a risk similar to that of never smokers after 15 years of cessation (5).

It is not yet clear how the risk of pancreatic cancer is affected by different aspects of smoking behavior. When we investigated which smoking aspect was most important in pancreatic cancer etiology by including smoking variables simultaneously in the model, only duration had a significant effect on pancreatic cancer risk. Accordingly, we concluded that duration seemed to affect pancreatic cancer risk the most in our cohort.

Not many studies included other aspects of smoking factors into a model, when examining smoking in relation to pancreatic cancer. Of the few studies that included smoking factors simultaneously in the model, however, all used a different model. Lynch et al. (5) adjusted for years of cessation in the analysis on number of cigarettes and duration, observing for both smoking factors an increased pancreatic cancer risk. Fuchs et al. (12) and Vrieling et al. (7) corrected for pack-years investigating the relation with time since quitting, observing risks comparable to that of never smokers after ≥10 and ≥5 years of quitting smoking, respectively. Vrieling et al. (7) also corrected for pack-years in the analyses on number of cigarettes and duration, observing similar risk estimates as for the model not including pack-years: a significant increased pancreatic cancer risk for number of cigarettes in current smokers, but no association for duration in current and former smokers. Jee et al. (37) corrected in a similar way we did, by including duration and frequency simultaneously in a model of current smokers. However, their results were different from ours: they observed a clear dose-response relation for frequency, but no association with duration in their Korean population.

However, when highly intercorrelated smoking factors are included simultaneously into a model, the problem of multi-collinearity may arise (39). In our analyses, some of the confidence intervals widened because some of the smoking variables were highly correlated (e.g., correlation of quitting smoking and duration, −0.71), which

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Table 1. Baseline characteristics (means or percent) of pancreatic cancer cases and subcohort members; Netherlands Cohort Study on diet and cancer (1986-2002)

Characteristics	Men		Women	
	Total pancreatic cancer cases	Subcohort	Total pancreatic cancer cases	Subcohort
n	280	2,191	240	2,247
Age, mean ± SD (y)	62.0 ± 3.9	61.3 ± 4.2	62.5 ± 4.3	61.4 ± 4.3
Use of tobacco products, *n* (%)				
Never tobacco smoker	14 (5.0)	201 (9.2)	124 (51.7)	1,312 (58.4)
Ever cigarette smoker	181 (64.6)	1,322 (60.3)	115 (47.9)	930 (41.4)
Ever cigar smoker	1 (0.4)	46 (2.1)	—	—
Ever pipe smoker	2 (0.7)	8 (0.4)	—	—
Ever cigar and pipe smoker	3 (1.1)	23 (1.0)	—	—
Ever cigarette and other type of tobacco smoker	79 (28.2)	591 (27.0)	1 (0.4)	5 (0.2)
Cigarette smoking features				
Smoking status, *n* (%)				
Never	20 (7.1)	278 (12.7)	124 (51.7)	1,312 (58.4)
Former smoker	128 (45.7)	1,130 (51.6)	50 (20.8)	463 (20.6)
Current smoker	132 (47.2)	783 (35.7)	66 (27.5)	472 (21.0)
Duration, mean ± SD (y)*	36.1 ± 11.9	33.7 ± 11.8	29.0 ± 12.2	27.8 ± 12.5
Frequency, mean ± SD (cigarettes/d)*	17.3 ± 11.5	17.0 ± 10.6	11.4 ± 8.0	11.4 ± 8.3
Age at first exposure, mean ± SD (y)*	17.3 ± 4.4	17.1 ± 3.8	23.3 ± 7.7	23.7 ± 8.9
Age at cessation, mean ± SD (y)*	48.2 ± 11.0	46.6 ± 10.2	49.2 ± 10.3	46.8 ± 11.1
Years since cessation, mean ± SD*	7.0 ± 10.4	8.8 ± 10.4	5.9 ± 9.7	7.0 ± 10.3
Inhalation, *n* (%)*				
No	57 (23.0)	385 (20.7)	57 (49.6)	424 (46.5)
Yes	191 (77.0)	1,478 (79.3)	58 (50.4)	487 (53.5)
Filter usage, *n* (%)*				
Filter-tipped	40 (20.9)	244 (17.4)	68 (70.8)	530 (72.0)
Non–filter-tipped	151 (79.1)	1,158 (82.6)	28 (29.2)	206 (28.0)
Tar, mean ± SD (mg/d)*	357.3 ± 237.3	348.0 ± 227.2	165.4 ± 149.1	156.8 ± 148.5
Nicotine, mean ± SD (mg/d)*	31.3 ± 25.7	30.2 ± 24.3	12.5 ± 11.1	12.3 ± 11.4
Passive smoking†				
Spouse smoking status, *n* (%)				
Never	12 (92.3)	128 (69.2)	21 (18.9)	182 (15.8)
Ever	1 (7.7)	57 (30.8)	90 (81.1)	972 (84.2)
Parental smoking, *n* (%)				
No parent smoked	1 (7.1)	47 (24.0)	20 (16.5)	193 (15.2)
One or both parents smoked	13 (92.9)	149 (76.0)	101 (83.5)	1,079 (84.8)
Passive smoking exposure at work (past or present), *n* (%)				
Low exposure	5 (41.7)	97 (53.3)	64 (71.1)	578 (60.0)
High exposure	7 (58.3)	85 (46.7)	26 (28.9)	386 (40.0)
Duration current passive smoking exposure, mean ± SD (h/d)	8.2 ± 4.7	3.7 ± 4.1	4.7 ± 5.5	4.4 ± 4.7
BMI, mean ± SD (kg/m^2)	25.2 ± 3.0	25.0 ± 2.6	25.5 ± 3.6	25.1 ± 3.6
Physical activity (nonoccupational), *n* (%)				
<30 min/d	50 (17.9)	396 (18.3)	57 (23.9)	553 (24.9)
30-60 min/d	94 (33.6)	675 (31.2)	77 (32.2)	691 (31.2)
60-90 min/d	66 (23.6)	405 (18.7)	62 (25.9)	498 (22.5)
>90 min/d	70 (25.0)	689 (31.8)	43 (18.0)	476 (21.5)
Family history of pancreatic cancer, *n* (%)	5 (1.8)	22 (1.0)	9 (3.8)	20 (0.9)

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Table 1. Baseline characteristics (means or percent) of pancreatic cancer cases and subcohort members; Netherlands Cohort Study on diet and cancer (1986-2002) (Cont'd)

Characteristics	Men		Women	
	Total pancreatic cancer cases	Subcohort	Total pancreatic cancer cases	Subcohort
History of diabetes, *n* (%)	21 (7.5)	75 (3.4)	10 (4.2)	80 (3.6)
History of hypertension, *n* (%)	58 (20.7)	512 (23.4)	73 (30.4)	662 (29.5)
Level of education, *n* (%)				
Low	132 (47.5)	997 (45.7)	137 (57.3)	1,266 (56.7)
Medium	89 (32.0)	775 (35.6)	83 (34.7)	771 (34.5)
High	57 (20.5)	408 (18.7)	19 (8.0)	197 (8.8)
Daily intake, mean ± SD				
Energy (kcal)	2,164 ± 466	2,166 ± 511	1,688 ± 397	1,686 ± 398
Total carbohydrates (g)‡	224.0 ± 38.5	226.7 ± 37.5	177.3 ± 26.8	178.8 ± 26.7
Total fat (g)‡	92.7 ± 13.4	93.9 ± 14.3	74.1 ± 10.9	74.0 ± 10.3
Alcohol (g)	18.0 ± 19.2	15.0 ± 16.8	6.6 ± 10.3	5.9 ± 9.5
Vegetables (g)	192.8 ± 86.1	191.6 ± 84.9	205.1 ± 85.4	195.5 ± 81.3
Fruit (g)	148.6 ± 120.6	154.0 ± 114.1	192.6 ± 107.8	196.4 ± 121.1

*Never smokers excluded.
†Ever smokers excluded.
‡Energy-adjusted intake.

indicates that multi-collinearity might have played a role to a certain degree.

After adjustment for duration, frequency, and smoking status, no association was observed for filter usage, inhalation, and exposure to tar and nicotine. Silverman et al. (10) observed an approximately 50% increased risk both for filter- and non–filter-tipped cigarettes compared with nonsmokers. Although they did not adjust for frequency or duration. As far as we know, no previous studies investigating pancreatic cancer risk in relation to nicotine and tar exposure have been conducted. For lung cancer, most epidemiologic studies showed an increased lung cancer risk after exposure to tar, including studies that adjusted for number of cigarettes smoked per day and duration of smoking (40).

The amounts of nicotine and tar were established using a smoking machine and were, besides the amount of nicotine in tobacco, dependent on cigarette design features such as type of filter, combustion rate, and paper porosity (41). The amount of nicotine to which a smoker is exposed is mainly dependent on the smoking behavior of the individual smoker, which is always focused on reaching a nicotine level in the blood that is satisfying for a smoker. Therefore, filter cigarettes or less nicotine per cigarette will probably lead to deeper inhalation, more cigarettes per day, or blocking the vents in the filter of a filter cigarette with the fingers or lips to establish the desired nicotine levels in the blood (41). This means that the exposure to tar and nicotine used in the present study, which were established by a smoking machine, might not reflect the real dose that the subjects in our cohort were exposed to. This may have influenced (most probably underestimated) our results. However, subjects smoking filter-tipped cigarettes were far less heavy smokers (≥20 cigarettes/d) than non–filter-tipped smokers (26.8% versus 43.8%, respectively).

It is not clear yet when smoking exerts its effects on the pancreatic carcinogenic process (1). Our smoking cessation results, together with results from other studies (5, 8, 10, 12, 38), might support more a late-stage mechanistic effect. However, we do not know the minimal time required for the carcinogenic process to occur for pancreatic cancer; it could take place in a relatively short amount of time (1).

Despite the fact that smoking is an established risk factor for pancreatic cancer, the mechanism behind this causal relation remains unclear. Nicotine itself is not carcinogenic; however, it is very addictive, resulting in a continuous exposure to a mixture of known (and unknown) carcinogens (42). The only pancreatic carcinogens known to be present in tobacco products are 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and its metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (42). NNK induced tumors of the pancreas when administered in drinking water to rats (43), and autopsy studies have shown substantial pancreatic tissue damage among smokers compared with nonsmokers (44). In addition, NNK levels in the pancreatic cancer juice of smokers were significantly higher than those in the juice of nonsmokers (45). Regarding tar, experimental evidence showed that tobacco tar could induce skin cancer in mice and rabbits (46).

It has been hypothesized that the solvent properties of alcohol may enhance the effects of exposure to

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carcinogens in tobacco (47). In a previous report, we reported that current smokers who consumed ≥30 g of ethanol/d experienced a HR of 2.4 (95% CI, 1.06-5.41) compared with abstainers who never smoked, when we investigated the interaction between ethanol intake and cigarette smoking (48). However, the interaction term was not found to be significant ($P_{interaction}$ = 0.97).

Similar to other previous studies (9, 14, 16, 17, 19), we did not find any association between passive smoking exposure and pancreatic cancer risk. However, three previous studies did observe a positive association for passive smoking. A prospective study in women, investigating both adult passive exposure and exposure during childhood, observed an increased risk only for maternal smoking (RR, 1.52; 95% CI, 0.97-2.39; ref. 18). A small Egyptian case-control study observed a positive association between adult passive exposure and pancreatic cancer risk (15). And a prospective study among Europeans observed an increased pancreatic cancer risk among never smokers who were exposed during childhood to passive smoking on a daily basis (HR, 2.61; 95% CI, 0.96-7.10) and a borderline statistically significant 54% increased risk for never smokers exposed to passive smoking at home and/or at work (7).

Environmental tobacco smoke is composed of sidestream smoke released by the burning tip of a cigarette or other smoking device and of mainstream smoke exhaled by the smoker (49). Sidestream smoke is the main component of this mixture and contains many of the same toxic constituents as mainstream smoke inhaled by smokers. However, sidestream smoke dilutes quickly; consequently, exposures to nonsmokers are much lower

Table 2. Age- and sex-adjusted and multivariable-adjusted HRs for pancreatic cancer according to cigarette smoking status, frequency, duration and time since cessation (categorical and continuous analyses), Netherlands Cohort Study on Diet and Cancer (1986-2002)

	All pancreatic cancer cases			
Cigarette smoking variable	**Person-years***	**No. of cases***	**Age- and sex-adjusted HR (95% CI)**	**Multivariable-adjusted† HR (95% CI)**
Smoking status				
Never‡	22,003	130	1.00	1.00
Former smoker	20,383	165	1.37 (1.05-1.78)	1.34 (1.02-1.75)
Current smoker	14,782	155	1.88 (1.44-2.44)	1.82 (1.40-2.38)
Frequency (cigarettes/d)				
Never‡	22,003	130	1.00	1.00
0.1 to <10	10,103	83	1.42 (1.05-1.91)	1.43 (1.06-1.93)
10 to <20	12,068	129	1.89 (1.42-2.52)	1.83 (1.37-2.45)
≥20	12,993	108	1.51 (1.12-2.04)	1.38 (1.01-1.87)
P for trend§			0.96	0.55
Continuous (increment of 10 cigarettes/d)			1.12 (1.03-1.23)	1.08 (0.98-1.19)
Duration (y)				
Never‡	22,003	130	1.00	1.00
0.1 to <20	6,693	47	1.29 (0.90-1.86)	1.30 (0.90-1.86)
20 to <40	16,965	130	1.41 (1.07-1.86)	1.38 (1.04-1.83)
≥40	11,507	143	2.13 (1.61-2.82)	2.03 (1.53-2.70)
P for trend§			0.01	0.02
Continuous (increment of 10 y)			1.16 (1.09-1.23)	1.15 (1.08-1.22)
Time since cessation				
Never‡	22,003	130	1.00	1.00
Quit ≥20 y	6,311	45	1.17 (0.81-1.71)	1.19 (0.81-1.73)
Quit 15 to <20 y	3,073	27	1.43 (0.89-2.27)	1.42 (0.89-2.27)
Quit 10 to <15 y	3,890	32	1.45 (0.95-2.22)	1.42 (0.92-2.18)
Quit 0.1 to <10 y	7,055	61	1.49 (1.06-2.08)	1.41 (1.00-1.98)
Current smoker	14,782	155	1.88 (1.45-2.44)	1.83 (1.40-2.39)
Continuous (increment of 10 y)§			0.85 (0.75-0.97)	0.87 (0.76-0.99)

*Number of cases and person-years do not add up to the total number because of missing values for covariables.
†Adjusted for age, sex, fruit intake (g/d), BMI (kg/m^2), and alcohol intake (g/d).
‡Reference group: never cigarette smokers.
§Never cigarette smokers excluded.

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Table 3. Age- and sex-adjusted and multivariable-adjusted HRs for pancreatic cancer according to inhalation, filter usage, and tar and nicotine exposure to cigarettes (categorical and continuous analyses), Netherlands Cohort Study on Diet and Cancer (1986-2002)

	All pancreatic cancer cases			
Exposure variable	**Person-years***	**No. of cases***	**Age- and sex-adjusted HR (95% CI)**	**Multivariable-adjusted HR (95% CI)**
Inhalation				
Never†	22,003	130	1.00	1.00‡
No	10,010	96	1.63 (1.23-2.17)	1.16 (0.75-1.81)
Yes	24,870	219	1.58 (1.22-2.06)	1.06 (0.64-1.78)
Filter usage				
Never†	22,003	130	1.00	1.00‡
Filter-tipped	9,756	93	1.74 (1.31-2.32)	1.06 (0.64-1.76)
Non–filter-tipped	16,701	155	1.61 (1.19-2.18)	1.02 (0.58-1.79)
Tar (mg/d)				
Never†	22,003	130	1.00	1.00§
0.1 to <200	9,406	91	1.72 (1.28-2.30)	0.88 (0.49-1.56)
200 to <400	6,616	65	1.75 (1.24-2.47)	0.77 (0.37-1.62)
≥400	5,089	53	1.85 (1.25-2.73)	0.79 (0.34-1.86)
P for trend‖			0.95	0.60
Continuous (increment of 100 mg/d)			1.08 (1.03-1.14)	1.05 (0.92-1.20)
Nicotine (mg/d)				
Never†	22,003	130	1.00	1.00§
0.1 to <10	6,078	53	1.55 (1.10-2.19)	0.87 (0.48-1.56)
10 to <20	4,973	49	1.78 (1.22-2.58)	0.94 (0.47-1.88)
20 to <30	3,752	41	1.97 (1.32-2.92)	0.99 (0.45-2.20)
≥30	6,407	67	1.88 (1.30-2.70)	0.96 (0.42-2.19)
P for trend‖			0.59	0.96
Continuous (increment of 10 mg/d)			1.07 (1.02-1.12)	1.02 (0.92-1.12)

*Number of cases and person-years do not add up to the total number because of missing values for covariables.
†Reference group: never cigarette smokers.
‡Adjusted for age, sex, fruit intake (g/d), BMI (kg/m^2), alcohol intake (g/d), frequency (cigarettes/d), duration (y), and current smoking status (yes/no).
§Adjusted for age, sex, fruit intake (g/d), BMI (kg/m^2), alcohol intake (g/d), duration (y), and current smoking status (yes/no).
‖Never cigarette smokers excluded.

than to smokers (49). Studies have shown that nonsmokers exposed to passive smoke take up and metabolize NNK, which provides experimental support for the hypothesis that passive smoking can cause smoking-related cancer (50). In addition, pooled analyses showed that spousal and workplace exposure to passive smoking was associated with a 20% to 25% excess risk of lung cancer (51).

In the current analysis, we were unable to adequately investigate pipe and cigar smoking because among never cigarettes smokers, only three cases ever smoked cigars or pipes and just 1.7% of all subcohort member smoked cigars or pipes only. Of the studies that have investigated pipe and cigar smoking in relation to pancreatic cancer (3, 14, 52), only three studies have been able to investigate pipe and cigar smoking separately, excluded lifelong cigarette smokers, or have been able to stratify by frequency or duration of pipe or cigar smoking (14, 52-54). Pooled estimates for pipe smoking showed a nonsignificantly increased pancreatic cancer risk of 39% whereas for cigar smoking, a significantly increased risk of 53% was observed (3).

The case-cohort approach was used because this is a more efficient design compared with a full-cohort analysis in which all questionnaires have to be entered before the analyses could be performed, whereas in the case-cohort approach, only the data for cases and subcohort members need to be entered. In our situation, this was most profitable because our questionnaire is very detailed and only the first page could be optically scanned. Also, another advantage is that exposure data can be processed during rather than after case ascertainment in comparison with a nested case-control design. One of the limitations of the case-cohort design is that

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Table 4. Age-adjusted and multivariable-adjusted HRs for pancreatic cancer according to passive smoking exposure in never-smoking women, Netherlands Cohort Study on Diet and Cancer (1986-2002)

	All pancreatic cancer cases			
Passive smoking	**Person-years***	**No. of cases***	**Age-adjusted HR (95% CI)**	**Multivariable adjusted† HR (95% CI)**
Spouse smoking status				
Never‡	2,625	20	1.00	1.00
Former smoker	8,055	46	0.72 (0.41-1.26)	0.67 (0.38-1.17)
Current smoker	6,198	42	0.87 (0.49-1.53)	0.78 (0.44-1.39)
Parental smoking				
No parents smoked‡	2,815	20	1.00	1.00
One or both parents smoked	15,645	97	0.91 (0.55-1.50)	0.90 (0.54-1.50)
Passive smoking exposure at work (past or present)				
Never‡	3,943	28	1.00	1.00
Occasionally exposed	4,611	34	1.10 (0.64-1.86)	1.08 (0.64-1.84)
Regularly or always exposed	5,600	25	0.64 (0.36-1.12)	0.61 (0.34-1.07)
Duration current passive smoking exposure (h/d; occupational and private)				
No exposure‡	5,463	34	1.00	1.00
>0 to <3	4,969	35	1.14 (0.70-1.87)	1.14 (0.70-1.88)
≥3	4,698	32	1.17 (0.70-1.95)	1.07 (0.64-1.80)
P for trend			0.64	0.93
Continuous (increment of 1 h/d)			1.02 (0.98-1.07)	1.01 (0.97-1.06)

*Missing values for passive smoking characteristics gave rise to diminished numbers of person-years and pancreatic cancer cases for the different passive smoking variables.

†Adjusted for age, BMI (kg/m^2), and level of education (primary school or lower vocational school/intermediate, vocational school or high school/higher vocational school, or college).

‡Reference group.

the variance estimates will not be as small as compared with a full cohort analysis, leading to slightly larger confidence intervals. Another disadvantage might be the difficulty of analyzing data in a case-cohort study; however, more and more statistical software packages, such as the statistical package we used (Intercooled STATA, version 9), which contains software for analysis of case-cohort data, are becoming available.

One of the limitations regarding the analysis on passive smoking is that we were unable to perform the analysis using individuals never exposed in any way to smoking as a reference group, as only one female case was never exposed to smoke. In addition, misclassification could have occurred because we did not have any information on the number of smokers and of cigarettes smoked, room volume, ventilation, and duration of the different exposures (49). Future studies should incorporate a more comprehensive and more accurate measure of passive smoking exposure. Another limitation of our study is that no information was collected about changes in cigarette smoking status during the follow-up period. After years of declining, especially among men, smoking rates leveled off in the late 1980s and have not changed until 2000 (55). Few people ages ≥50 years will start smoking, but more people will quit while aging (55). A substantial proportion of the cohort members might have stopped smoking during the 16 years of follow-up, although they would still be classified as current smokers in the current analysis. This may have resulted in an underestimation of the smoking effect.

The possibility to further restrict the analyses to microscopically verified cases only, in which misclassification by disease status would be less likely than among nonmicroscopically confirmed pancreatic cancer cases (32), was one of the strengths of this study. Other strengths include the large sample size and detailed information on potential risk factors of pancreatic cancer. Differential follow-up is unlikely to have made a material contribution to our findings because the completeness of follow-up was high (24). The prospective design avoided recall bias and the need to use next-of-kin respondents.

In summary, our findings confirmed that cigarette smoking is an important risk factor for pancreatic cancer, whereas quitting smoking reduced risk. Therefore, from a public health perspective, quitting smoking could decrease the incidence of pancreatic cancer. On the other hand, we did not observe any association between passive smoking exposure and pancreatic cancer risk in women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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