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Passive Smoking and Pancreatic Cancer in Women: a Prospective Cohort Study

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Abstract

Background—Active smoking is an established risk factor for pancreatic cancer, but the role of passive smoking in pancreatic carcinogenesis remains unclear. We aimed to examine whether environmental tobacco smoke is associated with pancreatic cancer risk.

Methods—We prospectively examined 86,673 women in the Nurses' Health Study. History of exposure to environmental tobacco smoke was assessed through questionnaires in 1982. Relative risks (RR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards models.

Results—During 24 years of follow-up (1982–2006), 384 women were diagnosed with pancreatic cancer. Maternal smoking significantly increased the risk of pancreatic cancer (RR, 1.42; 95% CI, 1.07–1.89), whereas paternal smoking was not related to the risk (RR, 0.97; 95% CI, 0.77–1.21). The risk associated with maternal smoking remained elevated, albeit not significant, among never smokers (RR, 1.52; 95% CI, 0.97–2.39). No association was found for adult passive exposure at work or at home.

Conclusions—The positive association with maternal smoking suggests that environmental tobacco smoke, potentially *in utero* or in early life, may be associated with pancreatic cancer.

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States (1). Cigarette smoking is one of the most important risk factors for pancreatic cancer, accounting for ~25% of all cases (2). Compared with nonsmokers, current smokers have a 2- to 3-fold elevated risk of developing pancreatic cancer (3). Secondhand smoke, also known as environmental tobacco smoke, contains many of the same carcinogenic compounds as the

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No potential conflicts of interest were disclosed.

mainstream smoke inhaled by active smokers (4). Therefore, passive smoking might also increase the risk of pancreatic cancer.

Despite major efforts to reduce smoking prevalence, ~15% of pregnant women in the United States still smoke (5). Recent studies have indicated that *in utero* exposure to tobacco smoke posts serious threats to the fetus and causes illnesses later in life, such as sudden infant death syndrome, asthma, and obesity (6). Studies of exposure to parental smoking have also suggested a possible link between *in utero* exposure to cigarette smoke and cancer development, although the overall findings are inconclusive (7).

The epidemiologic evidence for the role of passive smoking in pancreatic carcinogenesis is limited and inconsistent. Thus far, five studies have examined the relation of passive smoking to pancreatic cancer (8–12) and only one of them has a prospective design (8). Most of these studies had relatively small number of cases (8,10,11) and lacked data on potential confounding factors such as diabetes (8,11,12) and body mass index (BMI; refs. 8–11). We therefore examined the association between passive smoking and pancreatic cancer risk in a large prospective cohort of U.S. women with detailed information on history of passive smoking and other risk factors for pancreatic cancer. To our knowledge, this is the only study to date to have examined the association specifically for maternal smoking.

Materials and Methods

Study Population

The Nurses' Health Study was initiated in 1976 and included 121,700 U.S. nurses ages 30 to 55 y. Detailed information on individual characteristics and life-style including active smoking were obtained from questionnaires at baseline and biennially thereafter. The overall follow-up rate was over 90% through 2006.[6] Most of the deaths in this cohort were reported by family members or by the postal service in response to the follow-up questionnaires. In addition, the National Death Index was searched for nonrespondents, which has been shown to have a sensitivity of 98% (13).

For the present analysis, we excluded women who did not return the 1982 questionnaire and women with a history of cancer (other than nonmelanoma skin cancer) up to 1982, leaving a cohort of 86,673 women eligible. The study was approved by the Human Research Committee at Brigham and Women's Hospital.

Identification of Pancreatic Cancer

Women were asked to report medical conditions on the biennial follow-up questionnaires. Whenever a participant (or family members) reported a diagnosis of pancreatic cancer, we asked for permission to obtain related medical records or pathology reports. If the primary or secondary cause of death on the death certificate was a previously unreported pancreatic cancer case, we contacted a family member to obtain permission to retrieve medical records to confirm the diagnosis.

Between the return of the 1982 questionnaire and December 31, 2006, a total of 384 incident pancreatic cancer cases were identified. Eighty-six percent of cases were confirmed with medical records. Remaining cases were verified by a secondary source (e.g., death certificate, physician, or telephone interview of a family member). In the analysis, we examined associations including and excluding cases with missing medical records. Because

[6] http://www.channing.harvard.edu/nhs/index.php/history/

these two types of analyses yielded similar results, we included cases without medical record.

Assessment of Environmental Tobacco Smoke

In the 1982 questionnaire, women were asked to report on their exposure to secondhand smoke, both when they were children and currently. The questions included whether their mother, father, or both parents smoked while the study participants were living with their parents, whether they were currently exposed to secondhand smoke at home or at work, and how many years they had lived with a smoker as an adult.

Smoking History and Other Risk Factors

At baseline and in all subsequent questionnaires, women were asked about their history of active smoking, including smoking status, time since quitting, and average number of cigarettes smoked daily. They were also asked about history of diabetes at baseline and biennially thereafter. Participants reported their height and weight at baseline. Information on other risk factors of pancreatic cancer, including physical activity, intake of fruits and vegetables, alcohol consumption, multivitamin use, and aspirin use, was obtained from the 1980 questionnaire.

Statistical Analysis

We computed person-time from the return date of the 1982 questionnaire to the date of pancreatic cancer diagnosis, death from any cause, or the end of follow-up (December 31, 2006), whichever came first. Relative risks (RR) and 95% confidence intervals (CI) were estimated by Cox proportional hazards regression stratified by age (in months) and calendar time (in 2 y), thereby creating a time metric that simultaneously accounted for age and calendar time.

With those whose parents were nonsmokers serving as a comparison group, we computed RRs of pancreatic cancer for participants whose mother, father, or both parents were smokers. We then compared the risk among individuals who were currently exposed to secondhand smoke at work and / or at home with the risk among those without current passive exposure. Additionally, we categorized years living with smokers into four groups (<5, 5–19, 20–29, 30+) and estimated the RRs for long-term adult exposure to householder smoking.

In multivariate models, we adjusted for active cigarette smoking (never, quit ≥15 y, quit 5 to <15 y, quit <5 y, current <15 cigarettes / d, current 15–24 cigarettes / d, current 25+ cigarettes / d), diabetes (yes / no), height (quintiles), and BMI (quintiles), as these are either established or possible risk factors for pancreatic cancer. Further adjustment for other covariates, including physical activity, intake of fruits and vegetables, alcohol consumption, multivitamin use, and aspirin use, made little difference to risk estimates. An indicator variable for missing values of each covariate was created.

Because our data showed that women with passive exposure were more likely to be active smokers themselves and active smoking is an important risk factor for pancreatic cancer, we then restricted analysis to never-active smokers to minimize the confounding by active smoking. All *P* values were two-sided and the statistical procedures were done using SAS 9.1 (SAS Institute).

Results

Compared with those who were never exposed to other people's smoke, individuals with exposure to secondhand smoke during their lifetime were more likely to be ever active smokers themselves (RR, 2.43; $P < 0.001$). They were also more likely to have history of diabetes and tended to consume more alcohol (Table 1).

Overall, maternal smoking was associated with a statistically significant increase in risk for pancreatic cancer (RR, 1.42; 95% CI, 1.07–1.89; $P = 0.01$), whereas paternal smoking was not associated with risk (RR, 0.97; 95% CI, 0.77–1.21; Table 2). RR for smoking by both parents was 1.41 (95% CI, 1.03–1.91; $P = 0.03$). Current passive exposure at home and / or at work as reported in the 1982 questionnaire was not related to risk (Table 2). Similarly, long-term adult exposure to householder smoking did not increase the risk of pancreatic cancer (Table 2).

We restricted our analysis to never-active smokers (37,757 women; 151 cases) and observed that those who reported maternal smoking had an excess risk of pancreatic cancer, although the association was not significant (RR, 1.52; 95% CI, 0.97–2.39; $P = 0.06$; Table 3). Similarly, no statistically significant association was observed for paternal smoking (RR, 0.76; 95% CI, 0.54–1.07; Table 3) or smoking by both parents (RR, 1.32; 95% CI, 0.79–2.21). Adult passive exposure at work or at home as well as long-term adult exposure to householder smoking was unrelated to the risk (Table 3).

Discussion

In this prospective study, maternal smoking, but not paternal smoking, significantly increased the overall risk of pancreatic cancer in women. The risk associated with maternal smoking remained elevated, albeit not significant, among never smokers, which could be due to the small number of exposed individuals among never smokers. Adult exposure to environmental tobacco smoke was not related to the risk.

The observed association between maternal smoking and pancreatic cancer could be explained by several mechanisms. Carcinogens in environmental tobacco smoke, such as pancreas-specific nitosamine 4-(methylnitrosamino)-l-(3-pyridyl)-l-butanone and its major metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, are known to have genotoxic effects via formation of DNA adducts, causing gene mutations and stimulating cell proliferation (14). Recent research has also shown that tobacco smoke may act as a trigger for pancreatic carcinogenesis by inducing chronic inflammatory responses (15,16).

Individuals with a mother who smoked while they were living together were probably exposed to passive smoking *in utero* or very early childhood. In the Nurses' Health Study, the daughter's report of childhood exposure to maternal smoking (the Nurses' Health Study, the 1999 questionnaire) is a good proxy for mother's report of smoking during pregnancy (the Nurses' Mothers Cohort, the 2001 questionnaire), yielding 89% sensitivity and 88% specificity (6). Although the correlation might not be as strong in the 1980s given the growing concern about maternal smoking in recent years, it is still possible that the association between passive maternal smoking and increased pancreatic risk could reflect exposure *in utero* or an enhanced susceptibility during early developmental ages when the pancreas is increasing in size. Consistent with our findings, a summary report on childhood exposure and lung cancer reported a positive association with maternal smoking (RR, 1.50; 95% CI, 1.04–2.14), and a weaker association for paternal smoking (RR, 1.25; 95% CI, 0.94–1.68; ref. 17).

In addition, as children and their mothers usually have close contact and spend a lot of time together, exposure to maternal passive smoking might have relatively higher intensity and longer duration than exposure to paternal passive smoking or adult passive exposure. Although several case-control studies found a null association between passive exposure during childhood and pancreatic cancer risk (9,11,12), misclassification was likely to have been an issue because the questions asked were very vague (i.e., history of passive smoking during childhood [from birth to age 18 years (9), involuntary / passive smoking before age 20 years (11), and exposed to residential / occupational environmental tobacco smoke up to age 19 years (12)].

Alternatively, the positive association with maternal smoking might reflect heavy exposure where both parents smoked, as the majority (14,843 of 18,614; 80%) of women with exposure to maternal smoking were also exposed to paternal smoking. We observed a modest increase in risk of pancreatic cancer associated with smoking by both parents; however, the association became nonsignificant among never-active smokers, which might result from the limited statistical power of subgroup analyses.

The lack of an association between adult passive exposure and pancreatic cancer risk is consistent with three of four previous studies that assessed adult exposure to secondhand smoke (8,9,12); the positive association was only observed in a small Egyptian case-control study (10). Although adults might be less susceptible than children to the tumorigenic effect of smoke-derived carcinogens, the null results may be due to exposure misclassification as individual exposure to passive smoke is influenced by many factors, such as space volume, ventilation, and the actual time spent in tobacco smoke environment (4), and therefore is difficult to measure accurately.

The strengths of this study include prospective design and relatively detailed information on passive smoking. Residual confounding by active smoking is probably of minor importance as association patterns were similar among never smokers. Unmeasured confounding by family history of pancreatic cancer cannot be completely ruled out. However, family history of pancreatic cancer is uncommon and no evidence has linked it to maternal smoking. Misclassification of passive exposure is inevitable; however, it tends to be nondifferential and only bias the results toward the null. Because the present study only composed of women, we were not able to examine the association with passive smoking among men or whether the impact of maternal smoking would be different by gender. Finally, we were unable to estimate the risk for those who were only exposed to maternal smoking or for those who were only exposed to paternal smoking because of the substantial overlap between maternal smoking and paternal smoking. As a result, the observed associations could reflect greater exposure where both parents smoked, rather than a maternal / paternal difference. Even if this is true, the present findings still provide evidence for early exposure to secondhand smoke.

In summary, we observed a positive association between maternal smoking and risk of pancreatic cancer. Although we cannot exclude the possibility that this is a chance finding given the limited sample size among never smokers, the results suggest a potential role of early exposure to environmental tobacco smoke in pancreatic carcinogenesis. In addition to improving the accuracy of passive smoking measurement, future research needs to confirm the positive association with maternal smoking, particularly *in utero* exposure.

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Table 1

Age-standardized baseline characteristics of participants in the Nurses' Health Study (n = 86673) by childhood and adult exposure to passive smoking, 1982

	Parental smoking			Currently exposed at work or home	
Characteristic	**Neither parent**	**Mother***	**Father***	**None/Occasionally**	**Regularly**
No. of individuals	25,593	18,614	49,871	45,598	32,710
Age, y	48.9 (7.2)†	48.7 (7.2)	48.8 (7.2)	48.9 (7.3)	48.8 (7.2)
Height, inches	64.5 (2.4)	64.6 (2.5)	64.5 (2.4)	64.5 (2.4)	64.5 (2.5)
BMI, kg/m^2	23.7 (4.1)	23.7 (4.2)	23.8 (4.1)	23.6 (4.0)	24.0 (4.3)
History of type 2 diabetes, %	2.7	2.9	2.8	2.6	2.9
Ever smokers, %	46.4	68.0	59.8	49.1	65.1
Current alcohol drinker, %	58.5	71.5	66.7	64.1	64.7
Current multivitamin use, %	40.9	41.2	40.8	41.9	39.4
Current aspirin use, %	49.3	52.8	51.9	49.4	53.2

NOTE: Unknown parental smoking (n = 7438); unknown adult exposure (n = 8365).

*Included 14,843 women whose both parents were smokers.

†Mean (SD) for all such values.

Table 2

Passive smoking and risk of pancreatic cancer in the Nurses' Health Study (1982–2006)

Passive smoking	Cases	Person-years	Age-adjusted RR (95% CI)	Multivariable RR (95% CI)*
Parental smoking				
Neither parent	117	580,686	1.0 (Reference)	1.0 (Reference)
Mother†	93	425,299	1.54 (1.17–2.04)	1.42 (1.07–1.89)
Father†	211	1,129,815	1.02 (0.81–1.28)	0.97 (0.77–1.21)
Unknown	33	159,870	1.13 (0.77–1.67)	1.00 (0.68–1.48)
Currently exposed at work or home				
None	38	236,796	1.0 (Reference)	1.0 (Reference)
Occasionally	181	943,701	1.14 (0.83–1.56)	1.11 (0.81–1.52)
Regularly, work or home	73	356,846	1.16 (0.84–1.61)	1.01 (0.72–1.40)
Regularly, work and home	36	178,937	1.27 (0.83–1.94)	0.97 (0.63–1.51)
Unknown	56	240,420	1.36 (0.87–2.12)	1.17 (0.75–1.83)
Years lived with smoker as adult				
<5	116	691,234	1.0 (Reference)	1.0 (Reference)
5–19	86	504,792	1.04 (0.79–1.38)	0.99 (0.75–1.32)
20–29	71	346,066	1.03 (0.76–1.39)	0.91 (0.67–1.23)
30+	74	245,127	1.11 (0.82–1.51)	0.92 (0.67–1.26)
Unknown	37	169,480	1.19 (0.82–1.72)	1.02 (0.70–1.49)

*Multivariate models adjusted for age, height (quintiles), smoking (never, quit ≥15 y, quit 5 to <15 y, quit <5 y, current <15 cigarettes/d, current 15–24 cigarettes/d, current 25+ cigarettes/d), diabetes (yes/no), and BMI (quintiles).

†Included 14,843 women (70 cases) whose both parents were smokers.

Table 3

Passive smoking and risk of pancreatic cancer in the Nurses' Health Study 1982–2006, among never-active smokers

Passive smoking	Cases	Person-years	Age-adjusted RR (95% CI)	Multivariable RR (95% CI)*
Parental smoking				
Neither parent	65	312069	1.0 (Reference)	1.0 (Reference)
Mother†	30	143471	1.57 (1.01–2.46)	1.52 (0.97–2.39)
Father†	68	458754	0.77 (0.55–1.08)	0.76 (0.54–1.07)
Unknown	8	58464	0.68 (0.33–1.43)	0.64 (0.31–1.34)
Currently exposed at work or home				
None	18	129157	1.0 (Reference)	1.0 (Reference)
Occasionally	78	446664	0.84 (0.54–1.32)	0.81 (0.52–1.26)
Regularly, work or home	24	140198	1.21 (0.76–1.92)	1.13 (0.71–1.79)
Regularly, work and home	10	44866	1.30 (0.63–2.68)	1.13 (0.55–2.33)
Unknown	21	99351	0.79 (0.36–1.73)	0.71 (0.32–1.56)
Years lived with smoker as adult				
<5	66	433865	1.0 (Reference)	1.0 (Reference)
5–19	34	185236	1.17 (0.77–1.77)	1.17 (0.77–1.77)
20–29	20	108942	0.94 (0.57–1.56)	0.90 (0.54–1.49)
30+	22	70090	1.12 (0.68–1.85)	1.06 (0.64–1.75)
Unknown	9	62103	0.85 (0.42–1.71)	0.79 (0.39–1.60)

*Multivariate models adjusted for age, height (quintiles), diabetes (yes/no), and BMI (quintiles).

†Included 4,869 women (20 cases) whose both parents were smokers.