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*Original Article*

# Environmental tobacco smoke and pancreatic cancer: a case-control study

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**Abstract:** Background: It has been conformed that active smoking is an established risk factor for pancreatic cancer, but the role of environmental tobacco smok (passive smoking) in pancreatic cancer remains unclear. We intended to study the relationship between passive smoking and pancreatic cancer. Methods: From Oct. 1991 to Sep. 2014, A hospital-based case-control study on pancreatic cancer was conducted from the inpatient of five hospitals. 1076 cases pancreatic cancer patients. History of exposure to environmental tobacco smoke was assessed through questionnaires. Relative risks (RR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards models. Results: During 23 years of follow-up (1991-2014), 1076 patients were diagnosed with pancreatic cancer (686 men and 390 women). Compared to paternal smoking (RR, 0.97; 95% CI, 0.77-1.21; $P = 0.084$), maternal smoking significantly increased the risk of pancreatic cancer (R, 1.56; 95% CI, 1.13-1.98; $P = 0.018$). Although the risk associated with maternal smoking remained elevated compared to the never smokers (RR, 1.49; 95% CI, 1.07-2.27), there was no statistical significance. 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.

**Keywords:** Pancreatic cancer, smoking, case-control study

## Introduction

The mortality rate of pancreatic cancer in China was ranking the sixth among all cancers [1], and the fourth in the US [2]. It is a rapidly fatal malignancy with little effective treatment. One of the most important risk factors for pancreatic cancer is cigarette smoking, which accounted for 25% of all cases [3]. Compared with nonsmokers, smokers at present have a 2- to 3-fold elevated risk of developing pancreatic cancer [4]. Lin et al. has reported that Cigarette smoking is associated with an approximately 70% increase in the risk of death from pancreatic cancer [5]. Environmental tobacco smoke, also as second hand smoke (passive smoking), has many of the same carcinogenic compounds as the mainstream smoke inhaled by active smokers [6]. Therefore, passive smoking might also increase the risk to pancreatic cancer.

Studies have recently indicated that passive smoking in utero products serious threats to the fetus and causes illnesses later in life, for example: asthma, obesity and sudden infant death syndrome [7]. Studies of exposure to parental smoking have also suggested a possible link between passive smoking in utero and cancer development, although the overall findings are inconclusive [8].

The epidemiologic evidence for the role of passive smoking in pancreatic carcinogenesis is inconsistent and limited. No studies have addressed the role of passive smoking in pancreatic cancer among Chinese women. In the present study, we demonstrated the association between passive smoking and pancreatic cancer risk by a case-control study in Chinese cases with detailed information on the history of passive smoking for pancreatic cancer.

**Table 1.** Passive smoking and risk of pancreatic cancer in 1076 patients

| Passive smoking | Cases | Age-adjusted RR (95% CI) | Multivariable RR (95% CI)* |
|---|---|---|---|
| Parental smoking | | | |
| Neither parent | 218 | 1.0 (Reference) | 1.0 (Reference) |
| Mother | 180 | 1.63 (1.05-2.18) | 1.56 (1.13-1.98) |
| Father | 612 | 1.06 (0.83-1.31) | 0.98 (0.76-1.17) |
| Both parents | 113 | 1.12 (0.89-1.42) | 0.97 (0.83-1.26) |
| Unknown | 56 | 1.15 (0.77-1.58) | 1.00 (0.72-1.54) |
| Years lived with smoker as adult | | | |
| < 5 | 384 | 1.0 (Reference) | 1.0 (Reference) |
| 5-19 | 288 | 1.06 (0.73-1.42) | 1.02 (0.78-1.31) |
| 20-29 | 196 | 1.02 (0.74-1.37) | 0.94 (0.69-1.20) |
| > 30 | 163 | 1.13 (0.87-1.64) | 0.96 (0.72-1.35) |
| Unknown | 45 | 1.23 (0.84-1.81) | 1.04 (0.76-1.47) |

*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.

**Table 2.** Passive smoking and risk of pancreatic cancer among never-active smokers

| Passive smoking | Cases | Age-adjusted RR (95% CI) | Multivariable RR (95% CI)* |
|---|---|---|---|
| Parental smoking | | | |
| Neither parent | 186 | 1.0 (Reference) | 1.0 (Reference) |
| Mother | 80 | 1.54 (0.57-1.12) | 1.49 (1.07-2.27) |
| Father | 194 | 0.78 (0.56-1.10) | 0.76 (0.58-1.05) |
| Both parents | 76 | 1.36 (0.87-1.92) | 1.34 (0.81-2.19) |
| Unknown | 24 | 0.66 (0.36-1.45) | 0.65 (0.32-1.36) |
| Years lived with smoker as adult | | | |
| < 5 | 203 | 1.0 (Reference) | 1.0 (Reference) |
| 5-19 | 112 | 1.15 (0.79-1.78) | 1.15 (0.79-1.78) |
| 20-29 | 84 | 0.96 (0.61-1.59) | 0.93 (0.57-1.51) |
| > 30 | 68 | 1.11 (0.69-1.87) | 0.98 (0.67-1.74) |
| Unknown | 17 | 0.87 (0.51-1.78) | 0.82 (0.38-1.63) |

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

## Materials and methods

### *Patients*

Between Oct. 1991 to Sep. 2014, we performed a case-control study on pancreatic cancer in Linyi Cancer Hospital, China; People's Hospital of Zhangqiu, Jinan, China; Zhangqiu hospital of traditional Chinese medicine; Qilu Hospital, Jinan, China; People's Hospital of Henan, Zhengzhou, China; People's Hospital of Weifang. A total of 1076 patients with pancreatic cancer (686 men and 390 women) were included in the final analysis. All the patients were confired by histological or cytological confirmation. Most of the deaths were reported by family members in response to the follow-up questionnaires. All the patients' questionnaire was retured before 2014.

### *Assessment of environmental tobacco smoke*

In the questionnaire, patients or/their family members were asked to report on their exposure to second hand 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, and how many years they had lived with a smoker as an adult.

### *Smoking history*

The patients were asked about their history of active smoking, such as smoking status, time since quitting, and average number of cigarettes smoked daily.

### *Statistical analysis*

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. 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 adjust-

ed 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). All *P* values were two-sided and the statistical procedures were done using SPSS11.0

## Results

Maternal smoking was associated with a statistically significant increase in risk for pancreatic cancer (RR, 1.56; 95% CI, 1.13-1.98; *P* = 0.018), whereas paternal smoking was not associated with risk (RR, 0.97; 95% CI, 0.77-1.21; *P*=0.084; **Table 1**). RR for smoking by both parents was 0.97 (95% CI, 0.83-1.26; *P* = 0.076) (**Table 1**). Similarly, long-term adult exposure to householder smoking did not increase the risk of pancreatic cancer (**Table 1**).

We restricted our analysis to never-active smokers (484 cases) and observed that those who reported maternal smoking had an excess risk of pancreatic cancer, although the association was not significant [1.49 (1.07-2.27); *P* = 0.048; **Table 2**]. Similarly, no statistically significant association was observed for paternal smoking [0.76 (0.58-1.05); **Table 2**] or smoking by both parents (RR, 1.34; 95% CI, 0.81-2.19).

## Discussion

Our case-control study discussed the association between pancreatic cancer and passiving cigarette smoking. Our research confirmed that maternal smoking, but not paternal smoking, significantly increased the overall risk of pancreatic cancer. The risk associated with maternal smoking remained elevated, but not significant, among never smokers. Adult exposure to environmental tobacco smoke was not related to the risk.

Individuals with a mother who smoked while they were living together were probably exposed to passive smoking in utero or very early childhood which has increased risk of pancreatic cancer. 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.

Alternatively, the positive association with maternal smoking might reflect heavy exposure where both parents smoked, as the majority (76/80) of patients 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.

Despite the fact that passive smoking is an established risk factor for pancreatic cancer, the mechanism behind this causal relation remains unclear. 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 [9]. Recent research has also shown that tobacco smoke may act as a trigger for pancreatic carcinogenesis by inducing chronic inflammatory responses [10, 11].

In summary, we observed a positive association between maternal smoking and risk of pancreatic cancer.

The results suggest a potential role of early exposure to environmental tobacco smoke in pancreatic carcinogenesis. Maternal smoking inhibition is likely to be the only way to reduce the burden of pancreatic cancer.

## Disclosure of conflict of interest

None.

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