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Original article

Cigarette smoking and risk of pancreatic cancer: a clinic-based case-control study in the San Francisco Bay Area

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ABSTRACT

Purpose: Cigarette smoking is an established risk factor for pancreatic cancer (PC). We examined the association between cigarette smoking and PC in a San Francisco Bay Area clinic-based, case-control study.

Methods: A total of 536 cases and sex and age frequency-matched controls ($n = 869$) were recruited predominately from the University of California San Francisco (UCSF) medical clinics between 2006 and 2011. Participants were interviewed in-person using structured questionnaires. Adjusted odds ratios (ORs) were computed.

Results: Forty-eight percent of cases and controls reported never having smoked cigarettes; 39% of cases and 40% of controls were former smokers; 13% of cases and 12% of controls were current smokers. No association was found for either former (OR = 0.85, 95% confidence interval [CI] = 0.66–1.1) or current cigarette smoking (men: OR = 1.0, 95% CI = 0.60–1.7; women: OR = 1.2, 95% CI = 0.73–2.1). No dose-response relationships were detected with number of cigarettes/day, smoking intensity, duration, or years since last smoked. Comparisons with a 1995–1999 population-based UCSF study demonstrated a significantly increased proportion of never smokers in this study ($P < .001$).

Conclusions: This study revealed no significant associations between cigarette smoking and PC in the San Francisco Bay Area during 2006–2011. Data suggest a reduction in the duration of smoking within the referral population.

Introduction

In 2014, pancreatic cancer (PC) represented the fourth-leading cause of death from cancer among men and women in the United States, resulting in approximately 46,420 new cases and 39,590 deaths [1]. Fewer than 20% of patients present with localized, potentially curable tumors [2], primarily due to lack of disease-specific symptoms and methods for early detection [3,4]. In an earlier population-based case-control study of PC in the San Francisco Bay Area (SFBA), the 5-year survival rate was 1.5%, with a 10-month median survival time using active follow-up methods [5,6].

Cigarette smoking is an established risk factor for PC [3,7]. Multiple cohort and case-control studies, including ours [7] and three pooled or meta-analyses [8–10], have consistently demonstrated an association between PC and cigarette smoking, particularly among heavy smokers. In a pooled analysis of case-control studies [8], smoking 30 years or more conferred a two-fold risk and heavy smoking (more than 35 cigarettes per day) was associated with a three-fold risk for PC. An inverse dose-response relationship between years since quitting and PC was consistent with earlier summary analyses [9,10]. In our SFBA population-based, 1995–1999 PC case-control study, a nearly two-fold risk of PC was associated with current smoking and with 40 or more pack-years of smoking [7]. In addition, synergistic interaction was found with heavy smoking and polymorphisms in genes involved in tobacco carcinogen detoxification [11]. Pancreatic cancer risk among those who had quit smoking for 15 years or more was similar to that of nonsmokers [7–9].

Although cigarette smoking has steadily declined in California and in the SFBA [12–14], we hypothesized that it would remain associated with PC because of the relatively consistent associations across multiple study designs and settings [7–10]. In this report, we present findings from our 2006–2011 clinic-based, case-control study.

This analysis was conducted while a Visiting Professor at University of California San Francisco.

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Materials and methods

Participants

Details of study design and recruitment are provided elsewhere [15] and are summarized as follows.

Patients diagnosed with exocrine pancreatic adenocarcinoma between 2006 and 2011 were recruited predominantly from the University of California San Francisco (UCSF) Gastrointestinal Medical and Surgical Oncology clinics ($n = 463$), with supplemental recruitment from California Pacific Medical Center ($n = 46$, both located within San Francisco City and/or County [SFCC]), and the Cancer Prevention Institute of California's early case ascertainment in Santa Clara and San Mateo counties ($n = 27$). Thirteen percent of cases were residents of SFCC, 75% were from the SFBA, 7% were from outside SFBA, and 5% were from outside California. Eligible cases were 21–85 years of age at diagnosis and completed an in-person interview in English [15]. Diagnoses were confirmed using patients' medical records and the Surveillance Epidemiology and End Results abstracts that included histologic confirmation of diagnoses.

Controls were recruited from UCSF General Medicine Primary Care outpatient clinics, such as Internal Medicine and Family Medicine clinics located in SFCC. Approximately, 95% of controls resided in the six SFBA counties of San Francisco (67%), Alameda (10%), San Mateo (7%), Marin (6.5%), and Contra Costa (4%). The remainder of the controls resided outside the SFBA counties: 4% other Northern California, less than 1% Southern California, and 1% outside California. Typical reasons for clinic visits on recruitment day included annual physical, updating prescription medications, head cold, checking blood pressure, hypertension, depression, anxiety, fatigue, anemia, backache, and women's wellness visits. Controls, who did not receive incentives for participation, were approached in the waiting room of outpatient clinics and were not recruited from hospitalized inpatients or from outpatient surgical-treatment settings. Controls, recruited simultaneously to cases, were frequency matched by sex and age within 5-year age groups. Eligibility criteria for controls were the same as for cases with the exception of PC diagnosis. Of eligible controls, 35% refused to participate because of interview time; 536 cases and 869 controls were eligible and completed the interview (72% participation rate for eligible cases, 53% for eligible controls). The UCSF Committee on Human Research approved this study. Informed consent was obtained from each participant in the study.

Data collection

Data were collected during in-person (no proxy) interviews using an epidemiologic risk-factor questionnaire that included patient demographics, lifestyle factors, and personal and family medical history. Exposure data excluded one year before diagnosis (cases) or interview (controls). Height was self-reported as maximum adult height. Cigarette smoking was defined as 100 or more lifetime cigarettes. Cigar smoking was defined as 100 or more lifetime cigars. Pipe smoking was defined as 100 or more lifetime pipes. Chewing tobacco was ever having chewed tobacco once per day for one-year or more.

Analysis

Statistical analyses were conducted using SAS 9.3 (SAS Institute, Inc, Cary, NC). Descriptive analyses were conducted by case-control status using *t* tests and chi-square statistics. Body mass index (BMI) was computed using self-reported weight one-year before diagnosis (cases) or interview (controls) as weight/height^2 (kg/m^2). BMI used World Health Organization categories: underweight (less than 18.5), normal (18.5 to 24.9), overweight (25 to 29.9), and obese (30 or more). Owing to few participants in the underweight category ($n = 15$), the underweight and normal categories were combined for the BMI referent group. Data on lifetime weight-gain or weight-loss were not collected. Race was white/Caucasian, black/African American, Asian, or other. Education was: 12 years or more schooling, some college/completed college, or graduate school. Potential confounders included alcohol consumption (never, ever), Hispanic ethnicity (no, yes), diabetes (no, yes), pancreatitis (no, yes), and family history of cancer (no, yes).

The referent group for all analyses was participants who reported never having used any tobacco products. Nineteen men who reported use of cigars, pipes, or chewed tobacco were excluded from the referent group leaving 1386 study participants remaining in the analytic file. Cigarette smoking was analyzed as: never smoker, former, and current, average cigarettes per day (1–10, 11–20, more than 20), years smoked (1–10, 11–20, more than 20), and years since last smoked (former [more than 20, 11–20, 10 years or less ago] and current smoker). Intensity of smoking (pack-years) was cigarettes per day times numbers-of-years smoked and were grouped for analysis: 1–10, 11–20, more than 20. Former smokers were defined as those who had ceased smoking one year or more before interview. Current smokers also included 36 former smokers who reported having quit smoking within the immediate one year before interview and/or diagnosis. Eleven cases and eight controls had used cigar, pipe, or chewing tobacco; thus, a category for "other tobacco products" was compared with the referent group.

Odds ratios (OR) were computed using unconditional logistic regression models with 95% confidence intervals (CIs) adjusted for (1) age and sex only and (2) age, sex, race, education, BMI, alcohol, diabetes, pancreatitis, and family cancer history (fully adjusted model). If a response for any required data element was missing, the record associated with that missing data element was dropped from analysis. Linear trends in ORs were based on the Wald χ^2 statistic for the factor modeled as an ordinal variable. Effect modification by sex was explored in stratified analyses [15]. All statistical tests were two-sided and considered statistically significant when $P < .05$.

We examined differences in smoking status from the earlier population-based SFBA case-control study (PanC1, 1995–1999) [7] and the current clinic-based study (PanC2, 2006–2011) with tests for differences in two proportions by case groups and control groups. Using categories from the PanC1 study, groupings for the smoking-related variables (average cigarettes per day, years smoked, and pack-years) were: less than 20, 20–39, and 40 or more. BMI categories used in the earlier PanC1 for men were less than 23.1, 23.1 to less than 25.1, 25.1 to less than 27.1, and 27.1 or more; and for women were less than 21.5, 21.5 to less than 23.4, 23.4 to less than 25.8, and 25.8 or more [7].

Results

Among 1386 participants (525 cases and 861 controls), the mean age at interview was 61 years (range, 30–86 years). More than 80% of the study population was white, and more than 50% had completed some college. Female controls had the largest proportion of obese participants followed by male cases. 49% of cases and controls never smoked cigarettes; 39% of cases and 40% of controls were former smokers, and 13% of cases and 12% of controls were current smokers. No women reported using noncigarette tobacco products. Cases and controls were similar in mean smoking duration and cigarettes per day (Table 1). Limited variation was found by case-control status for categories of cigarettes per day and years of