RESEARCH ARTICLE

Cigarette Smoking and Pancreatic Cancer Risk: A Revisit with an Assessment of the Nicotine Dependence Phenotype

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Abstract

Background: Cigarette smoking is a well-established risk factor of pancreatic cancer (PC). Although an association between nicotine dependence phenotype, namely time to first cigarette (TTFC) after waking, and the risk of several smoking-related cancers has been reported, an association between TTFC and PC risk has not been reported. We assessed the impact of smoking behavior, particularly TTFC, on PC risk in a Japanese population. Materials and Methods: We conducted a case-control study using 341 PC and 1,705 non-cancer patients who visited Aichi Cancer Center in Nagoya, Japan. Exposure to risk factors, including smoking behavior, was assessed from the results of a self-administered questionnaire. The impact of smoking on PC risk was assessed with multivariate logistic regression analysis adjusted for potential confounders to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Results: Cigarettes per day (CPD) and/or smoking duration were significantly associated with PC risk, consistent with previous studies. For TTFC and PC risk, we found only a suggestive association: compared with a TTFC of more than 60 minutes, ORs were 1.15 (95%CI, 0.65- 2.04) for a TTFC of 30-60 minutes and 1.35 (95%CI, 0.85-2.15) for that of 0-30 minutes (p trend=0.139). After adjustment for CPD or smoking duration, no association was observed between TTFC and PC. Conclusions: In this study, we found no statistically significant association between TTFC and PC risk. Further studies concerning TTFC and PC risk are warranted.

Keywords: Pancreatic cancer - smoking - nicotine - addiction

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Introduction

Cigarette smoking is widely known as a risk factor of pancreatic cancer (PC) (Lin et al., 2001; IARC, 2004; Matsuo et al., 2011; Bosetti et al., 2012). We previously showed that cigarette smoking moderately increased the risk of PC in a Japanese population (Inoue et al., 2003; Matsuo et al., 2011). Although the effect of cigarettes per day (CPD) and/or smoking duration on cancer development can be detected in even a small study, a self-reported smoking behavior like pack-years (PY) is nevertheless only a proxy measure for the smoking uptake.

Recently, several studies reported that a shorter time to first cigarette (TTFC) after waking is associated with an increased risk of head and neck cancer, lung cancer, and esophageal cancer independently of CPD and/or smoking duration (Muscat et al., 2011a; 2011b; Matsuo et al., 2012; Muscat et al., 2012). TTFC is reported to reflect behavioral traits of nicotine addiction, including smoking amount, tolerance, difficulty in smoking cessation, and smoking relapse (Kabat and Wynder, 1987; Heatherton et al., 1989; Kozlowski et al., 1994; Pillitteri et al., 1997; Toll et al., 2007). Unlike conventional smoking parameters, such as CPD, smoking duration, PY, and years since quitting smoking, however, the association between TTFC and PC risk has not been evaluated.

Here, we assessed whether shorter TTFC predicts PC risk independently of CPD and/or smoking duration in a Japanese population. In addition, we revisited the associations between conventional smoking parameters and PC risk in the same study population.

Materials and Methods

Study subjects

Cases and controls were selected from the database of HERPACC-II, which is managed at Aichi Cancer Center Hospital (ACCH). Cases were 341 PC patients with no prior history of cancer, while controls were 1,705 non-cancer outpatients who were randomly selected and matched by sex and age (±3 years) to each case in a 1:5 case-control ratio. The framework of the HERPACC

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studies has been described elsewhere (Tajima et al., 2000; Hamajima et al., 2001). In brief, patients in HERPACC-II were enrolled between January 2001 and November 2005. All first-visit ACCH patients aged 20-79 years were asked to complete a self-administered questionnaire regarding their lifestyle before development of the current symptoms. Questionnaire responses were checked by trained interviewers. More than 95% of eligible patients completed the questionnaire. All data were loaded into the HERPACC database, which is periodically synchronized with the hospital cancer registry system. Approximately 35% of subjects in HERPACC-II were diagnosed with cancer within a year of first visit. In our study, we defined case subjects as patients who were diagnosed with PC within a year of first visit; that is, we considered time lag between first visit and final diagnosis of PC rather than prospectively identifying cases. Our previous study showed that the lifestyle patterns of first-visit outpatients to ACCH correspond with those of individuals randomly selected from Nagoya's general population, confirming the external validity of the study (Inoue et al., 1997b). The present study was approved by the Ethics Committee of Aichi Cancer Center and informed consent was obtained at first visit from all participants.

Assessment of exposure

Exposure to potential risk factors for PC was assessed from responses to the self-administered questionnaire, which were completed before diagnosis during the first visit to ACCH and checked by trained interviewers. All subjects were questioned about their lifestyle before the onset of the symptoms which impelled their visit to ACCH. Daily alcohol consumption in grams was calculated by summing the pure alcohol amount in the average daily consumption of Japanese sake (rice wine), shochu (distilled spirit), beer, wine and whiskey. Height and body weight before the onset of symptoms and weight at age 20 years were self-reported. Body mass index (BMI) was calculated by dividing the weight in kilograms by the height in meters squared, and expressed as kg/m^2. Family history of PC was considered positive when at least one parent or sibling had a history of PC.

Regarding smoking exposure, we categorized smoking status as never, former, and current smoking, and the latter two were further divided by the number of CPD (>0-19, ≥20-29, ≥30-39, ≥40), duration (>0-19, ≥20-29, ≥30-39, ≥40 years), PY of smoking (>0-19, ≥20-39, ≥40), and TTFC (>0-29, ≥30-59, ≥60 minutes). PY is the product of the average number of packs per day and the number of years of smoking. Former smokers were defined as subjects who had quit smoking for at least 1 year, and were further divided by duration since quitting (1-9, ≥10 years).

Statistical analysis

Differences in characteristics between cases and controls were tested using the chi-squared test. To assess the strength of the associations between smoking and PC risk, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression models adjusted for potential confounders although analyses about TTFC and PC risk in ever-smokers were conducted using unconditional logistic model to increase statistical power. Potential confounders considered in multivariate analysis were age, sex, current BMI (<18.5, ≥18.5-22, ≥22.5-24.5, ≥25-27, or ≥27.5 kg/m^2), BMI at age 20 (<18.5, ≥18.5-22, ≥22.5-24.5, ≥25-27, or ≥27.5 kg/m^2), drinking habit (non-drinker, <23, ≥23-45, or ≥46 g/day), history of diabetes mellitus (yes or no), and family history of PC (yes or no). All analyses were carried out using Stata version 10 (Stata Corp., College Station, TX, US), and P-values less than 0.05 were considered statistically significant.

Results

Background characteristics of all subjects are shown in Table 1. Age and sex were exactly matched between the cases and controls. Compared to the control group, the case group had a lower current BMI (p=0.073), higher BMI at age 20 (p<0.001), and higher prevalence of a history of diabetes mellitus (p<0.001). The distribution of other characteristics was similar, including drinking status and family history of PC.

Table 2 shows adjusted ORs and their 95% CIs of PC according to smoking behavior. Compared with never smokers, the OR for current smokers was 2.16 (95%CI, 1.54-3.03) and that for former smokers was 1.59 (95%CI, 1.10-2.32). In former smokers, those who had a long duration (≥10 years) since quitting smoking showed a tendency toward the null (OR=1.29, 95%CI: 0.78-2.14).

Table 1. Distribution Comparison of Pancreatic Cancer Patients and Controls with Respect to Selected Characteristics

		Case (%) n=341	Control (%) n=1705	p values**
Age	<40	15 (4.4)	72 (4.2)	0.999
	≥40-49	33 (9.7)	162 (9.5)	
	≥50-59	114 (33.4)	562 (33.0)	
	≥60-69	117 (34.3)	591 (34.7)	
	≥70	62 (18.2)	318 (18.7)	
Sex	Male	234 (68.6)	1,170 (68.6)	1.000
	Female	107 (31.4)	535 (31.4)	
Current BMI* (kg/m^2)	<18.5	28 (8.2)	104 (6.1)	0.073
	≥18.5-22	152 (44.6)	649 (38.1)	
	≥22.5-24.5	94 (27.6)	556 (32.6)	
	≥25-27	41 (12.0)	258 (15.1)	
	≥27.5	22 (6.5)	125 (7.3)	
	Unknown	4 (1.2)	13 (0.8)	
BMI* at age 20 (kg/m^2)	<18.5	22 (7.6)	208 (12.2)	<0.001
	≥18.5-22	206 (60.5)	1,090 (63.9)	
	≥22.5-24.5	70 (19.5)	295 (17.3)	
	≥25-27	15 (6.0)	51 (3.0)	
	≥27.5	9 (3.2)	23 (1.4)	
	Unknown	19 (3.2)	38 (2.2)	
Drinking (g ethanol/day)	Non	111 (32.6)	649 (38.1)	0.399
	<23	92 (27.0)	444 (26.0)	
	≥23-45	78 (22.9)	348 (20.4)	
	≥46	56 (16.4)	246 (14.4)	
	Unknown	4 (1.2)	18 (1.1)	
History of diabetes mellitus	Yes	56 (16.4)	139 (8.2)	<0.001
	No	285 (83.6)	1,566 (91.9)	
Family history of PC	Yes	14 (4.1)	62 (3.6)	0.676
	No	327 (95.9)	1,643 (96.4)	

*BMI: body mass index. **p values were calculated by Chi-squared test

Table 2. Adjusted Odds Ratios (ORs)* and 95% Confidence Intervals (CI) for Pancreatic Cancer and Smoking Habit

	Case (n)	Control (n)	ORs (95% CI)
Smoking status			
Never	115	757	1 (Reference)
Ever	226	945	1.91 (1.39-2.63)
Former (years)	84	443	1.59 (1.10-2.32)
quit for ≥1-9	37	124	2.59 (1.47-4.58)
quit for ≥10	47	319	1.29 (0.78-2.14)
Current	142	502	2.16 (1.54-3.03)
Unknown	0	3	
Pack-years of smoking (p trend<0.001)			
>0-19	53	268	1.58 (1.07-2.35)
≥20-39	62	311	1.66 (1.10-2.48)
≥40	109	355	2.72 (1.86-3.99)
Unknown	2	14	
Smoking duration (years) (p trend<0.001)			
>0-19	39	222	1.37 (0.87-2.14)
≥20-29	41	183	1.91 (1.22-2.98)
≥30-39	74	290	2.20 (1.45-3.33)
≥40	70	241	2.40 (1.56-3.71)
Unknown	2	12	
Smoking frequency (cigarettes/day) (p trend<0.001)			
>0-19	54	279	1.44 (0.97-2.14)
≥20-29	86	353	2.13 (1.46-3.11)
≥30-39	35	128	2.45 (1.51-4.00)
≥40	50	177	2.55 (1.62-4.01)
Unknown	1	11	
Time to first cigarette (min) (p trend<0.001)			
>0-29	162	612	2.08 (1.48-2.91)
≥30-59	35	165	1.77 (1.11-2.82)
≥60	26	142	1.54 (0.93-2.55)
Unknown	3	29	

*Conditional logistic regression model adjusted for current BMI, BMI at age 20, drinking habit, diabetes mellitus, and family history of PC

Table 3. Odds Ratios (ORs) and 95% Confidence Intervals (CI) for Pancreatic Cancer and Time to First Cigarette in Ever-Smokers

	Age, sex-adjusted ORs (95% CI)	Multivariable-adjusted ORs* (95% CI)
Time to first cigarette (min)		
≥60	1 (Reference)	1 (Reference)
≥30-59	1.19 (0.68-2.08)	1.15 (0.65-2.04)
>0-29	1.48 (0.94-2.34)	1.35 (0.85-2.15)
p trend	0.065	0.139
Adjusted for pack-years‡		
≥60	1 (Reference)	1 (Reference)
≥30-59	1.12 (0.63-1.99)	1.08 (0.60-1.94)
>0-29	1.21 (0.73-2.00)	1.09 (0.65-1.83)
p trend	0.326	0.490
Adjusted for total years§		
≥60	1 (Reference)	1 (Reference)
≥30-59	1.11 (0.63-1.95)	1.07 (0.60-1.90)
>0-29	1.25 (0.78-2.01)	1.17 (0.72-1.89)
p trend	0.280	0.355
Adjusted for cigarettes per day†		
≥60	1 (Reference)	1 (Reference)
≥30-59	1.11 (0.63-1.96)	1.05 (0.58-1.87)
>0-29	1.29 (0.79-2.10)	1.12 (0.68-1.85)
p trend	0.170	0.324
Adjusted for smoking status¶		
≥60	1 (Reference)	1 (Reference)
≥30-59	1.16 (0.66-2.03)	1.12 (0.64-1.99)
>0-29	1.34 (0.84-2.13)	1.24 (0.77-1.99)
p trend	0.213	0.315
Adjusted for years since quitting††		
≥60	1 (Reference)	1 (Reference)
≥30-59	1.10 (0.63-1.94)	1.08 (0.61-1.91)
>0-29	1.26 (0.79-2.01)	1.18 (0.73-1.91)
p trend	0.325	0.437

*Unconditional logistic regression model adjusted for age, sex, current BMI, BMI at age 20, drinking habit, diabetes mellitus, and family history of PC. ‡Pack-years (PY): 0-19, 20-39, ≥40. §Total years: <20 years, 20-29 years, 30-39 years, ≥40 years. †Cigarettes per day: 0-19, 20-29, 30-39, ≥40 cigarettes. ¶Smoking status: ever or current. ††Years since quitting: ≥10 years, 1-9 years, current

Regarding other conventional smoking parameters, an elevated risk of PC was observed with increasing PY (p trend<0.001), smoking duration (years, p trend<0.001), and CPD (p trend<0.001). A significant association was also seen between shorter TTFC and increased risk of PC compared with never smokers (p trend<0.001).

Compared with a TTFC of more than 60 minutes, unadjusted ORs in ever smokers were 1.19 (95% CI, 0.68-2.08) for a TTFC of 30-60 minutes and 1.48 (95%CI, 0.94-2.34) for that of 0-30 minutes (p trend=0.065) (Table 3). ORs adjusted by potential confounders without smoking were 1.15 (95%CI, 0.65-2.04) for TTFC of 30-60 minutes and 1.35 (95%CI, 0.85-2.15) for that of 0-30 minutes (p trend=0.139). After adjustment for conventional smoking parameters, such as PY, smoking duration, CPD and years since quitting smoking, no association was seen between TTFC and PC risk.

Discussion

Our case-control study confirmed our previous findings that cigarette smoking is significantly associated with an increased risk of PC in Japanese. We also evaluated the association between TTFC and PC risk, but found only a suggestive association between them. To our knowledge, this is the first study to evaluate the association of TTFC with PC risk.

Although cigarette smoking is probably a weak PC carcinogen, smoking behavior has been consistently reported to be associated with an increased risk of PC (Lin et al., 2001; IARC, 2004; Matsuo et al., 2011; Bosetti et al., 2012). Compared to never or non-smokers, odds ratios for current smokers in previous case-control studies has ranged from 1.4 to 5.7 (Lin et al., 2001). A meta-analysis of Japanese studies calculated a summary estimate for ever smoking relative to never smoking of 1.68 (95%CI, 1.38-2.05) (Matsuo et al., 2011). We therefore consider our findings to be consistent with previous studies. In addition, our study showed that after quitting smoking for more than ten years, the PC risk for ever smokers was almost identical to that for never smokers. Several other studies have also reported a risk reduction of PC after smoking cessation (Silverman et al., 1994; Fuchs et al., 1996; Muscat et al., 1997; Partanen et al., 1997; Nilsen and Vatten, 2000), and together suggest a modest but rigid causal relationship between smoking and PC, as well as the importance of smoking cessation for people at high risk of PC.

TTFC is one determinant of the nicotine dependence phenotype. The "low" dependent phenotype are smokers who smoke >30 minutes after waking and ≤20 cigarettes per day, and the "high" dependent phenotype are smokers who smoke ≤30 minutes after waking (Muscat et al., 2009). In addition, TTFC is thought to reflect the intensity of smoking, such as the depth and frequency of

puffing, which has not been satisfactorily measured by conventional smoking parameters (Matsuo et al., 2012; Muscat et al., 2012). Recently, an association was reported between TTFC and smoking-related cancers, namely lung cancer and upper aero-digestive tract (UADT) cancer (Muscat et al., 2011a; 2011b; 2012; Matsuo et al., 2012). Although PC is also a smoking-related cancer, we were unable to detect a statistically significant association between TTFC and PC risk. Since the association of smoking with PC is not as strong as that with lung or UADT cancer (Lin et al., 2001; 2002; Inoue et al., 2003; Polesel et al., 2008; Lee et al., 2012), TTFC may be less strongly associated with the risk of PC. Confirmation of our findings awaits further investigation in a larger study.

This case-control study has several methodological issues and limitations which warrant mention. First, control subjects were selected from non-cancer patients at ACCH. We consider that this was the same population from which the case subjects arose, which would warrant the internal validity of this study. Second, regarding external validity, we previously confirmed that randomly selected subjects from our control population were similar to the general population of Nagoya City in terms of the exposure of interest (Inoue et al., 1997a). Nonetheless, the medical background of the controls would remain the potential souse of bias. In this regard, our previous study in women demonstrated that this matter had only limited impact: more than 66% of non-cancer outpatients at ACCH have no specific medical condition, while the remaining 34% have specific diseases such as benign tumors, non-neoplastic polyps or both (13.1%), mastitis (7.5%), gastrointestinal disease (4.1%), or benign gynecologic disease (4.1%) (Kanda et al., 2009; Kawase et al., 2009). The situation for men is thought to be comparable. Third, case-control studies have an intrinsic information bias. However, the HERPACC system is less prone to this bias than typical hospital-based case-control studies as the data for all participants are collected before diagnosis. In addition, responses to self-administered questionnaires may be inaccurate and provide considerable variation. Any such misclassification would be non-differential, however, and would likely underestimate the causal association (Suzuki et al., 2008). Fourth, residual confounding by known and unknown risk factors might have been present; and given the modest number of cases, our findings require replication in larger studies. Last, this study was limited to a Japanese population, and the results cannot necessarily be extrapolated to other populations.

In conclusion, our study reconfirmed the association between conventional smoking parameters and the risk of PC. We did not detect a statistically significant association between TTFC and PC risk. A comprehensive understanding of the association between TTFC and PC risk awaits further studies in a variety of ethnic groups.

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