

## RESEARCH ARTICLE

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

Makoto Nakao<sup>1,2</sup>, Satoyo Hosono<sup>1</sup>, Hidemi Ito<sup>1</sup>, Isao Oze<sup>1</sup>, Miki Watanabe<sup>1</sup>, Nobumasa Mizuno<sup>3</sup>, Yasushi Yatabe<sup>4</sup>, Kenji Yamao<sup>3</sup>, Akio Niimi<sup>2</sup>, Kazuo Tajima<sup>1</sup>, Hideo Tanaka<sup>1,5</sup>, Keitaro Matsuo<sup>1,5\*</sup>

## 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

*Asian Pac J Cancer Prev*, 14 (7), 4409-4413

## 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 ( $\pm 3$  years) to each case in a 1:5 case-control ratio. The framework of the HERPACC

<sup>1</sup>Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, <sup>2</sup>Department of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Sciences, <sup>3</sup>Department of Gastroenterology, Aichi Cancer Center Hospital, <sup>4</sup>Department of Pathology and Molecular Diagnostics, Aichi Cancer Center Hospital, <sup>5</sup>Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan \*For correspondence: [kmatsuo@aichi-cc.jp](mailto:kmatsuo@aichi-cc.jp)

studies has been described elsewhere (Tajima et al., 2000; Hamajima et al., 2001). In brief, patients in HEPACC-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 HEPACC database, which is periodically synchronized with the hospital cancer registry system. Approximately 35% of subjects in HEPACC-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<sup>2</sup>. 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<sup>2</sup>), BMI at age 20 (<18.5, ≥18.5-22, ≥22.5-24.5, ≥25-27, or ≥27.5 kg/m<sup>2</sup>), 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 <sup>2</sup> )	<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)	
BMI* at age 20 (kg/m <sup>2</sup> )	Unknown	4 (1.2)	13 (0.8)	<0.001
	<18.5	22 (7.6)	208 (12.2)	
	≥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)	
Drinking (g ethanol/day)	≥27.5	9 (3.2)	23 (1.4)	0.399
	Unknown	19 (3.2)	38 (2.2)	
	Non	111 (32.6)	649 (38.1)	
	<23	92 (27.0)	444 (26.0)	
	≥23-45	78 (22.9)	348 (20.4)	
History of diabetes mellitus	≥46	56 (16.4)	246 (14.4)	<0.001
	Unknown	4 (1.2)	18 (1.1)	
	Yes	56 (16.4)	139 (8.2)	
	No	285 (83.6)	1,566 (91.9)	
	Family history of PC	Yes	14 (4.1)	
	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)
<b>Smoking status</b>			
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 $\geq 1-9$	37	124	2.59 (1.47-4.58)
quit for $\geq 10$	47	319	1.29 (0.78-2.14)
Current	142	502	2.16 (1.54-3.03)
Unknown	0	3	
<b>Pack-years of smoking (p trend&lt;0.001)</b>			
>0-19	53	268	1.58 (1.07-2.35)
$\geq 20-39$	62	311	1.66 (1.10-2.48)
$\geq 40$	109	355	2.72 (1.86-3.99)
Unknown	2	14	
<b>Smoking duration (years) (p trend&lt;0.001)</b>			
>0-19	39	222	1.37 (0.87-2.14)
$\geq 20-29$	41	183	1.91 (1.22-2.98)
$\geq 30-39$	74	290	2.20 (1.45-3.33)
$\geq 40$	70	241	2.40 (1.56-3.71)
Unknown	2	12	
<b>Smoking frequency (cigarettes/day) (p trend&lt;0.001)</b>			
>0-19	54	279	1.44 (0.97-2.14)
$\geq 20-29$	86	353	2.13 (1.46-3.11)
$\geq 30-39$	35	128	2.45 (1.51-4.00)
$\geq 40$	50	177	2.55 (1.62-4.01)
Unknown	1	11	
<b>Time to first cigarette (min) (p trend&lt;0.001)</b>			
>0-29	162	612	2.08 (1.48-2.91)
$\geq 30-59$	35	165	1.77 (1.11-2.82)
$\geq 60$	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

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

**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)
<b>Time to first cigarette (min)</b>		
$\geq 60$	1 (Reference)	1 (Reference)
$\geq 30-59$	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
<b>Adjusted for pack-years<sup>‡</sup></b>		
$\geq 60$	1 (Reference)	1 (Reference)
$\geq 30-59$	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
<b>Adjusted for total years<sup>§</sup></b>		
$\geq 60$	1 (Reference)	1 (Reference)
$\geq 30-59$	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
<b>Adjusted for cigarettes per day<sup>†</sup></b>		
$\geq 60$	1 (Reference)	1 (Reference)
$\geq 30-59$	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
<b>Adjusted for smoking status<sup>¶</sup></b>		
$\geq 60$	1 (Reference)	1 (Reference)
$\geq 30-59$	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
<b>Adjusted for years since quitting<sup>**</sup></b>		
$\geq 60$	1 (Reference)	1 (Reference)
$\geq 30-59$	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. <sup>‡</sup>Pack-years (PY): 0-19, 20-39,  $\geq 40$ . <sup>§</sup>Total years: <20 years, 20-29 years, 30-39 years,  $\geq 40$  years. <sup>†</sup>Cigarettes per day: 0-19, 20-29, 30-39,  $\geq 40$  cigarettes. <sup>¶</sup>Smoking status: ever or current. <sup>\*\*</sup>Years since quitting:  $\geq 10$  years, 1-9 years, current

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  $\leq 20$  cigarettes per day, and the "high" dependent phenotype are smokers who smoke  $\leq 30$  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 source 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.

## Acknowledgements

The authors gratefully acknowledge the efforts and contribution of doctors, nurses, technical staff, and hospital administration staff at Aichi Cancer Center for the daily management of the HERPACC study.

This study was supported by a Grant-in-Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science and Technology of Japan; a Grant-in-Aid from the National Cancer Center Research and Development Fund (H21-11-01); Health and Labour Sciences Research Grants for Research on Applying Health Technology (No. 201136002A) from the Ministry of Health, Labor and Welfare; a Grant-in-Aid for Scientific Research on Priority Areas of Cancer (No. 17015018) and on Innovative Areas (No. 221S0001) from the Japanese Ministry of Education, Culture, Sports, Science and Technology; and the Japan Society for the Promotion of Science A3 Foresight Program.

## References

- Bosetti C, Lucenteforte E, Silverman DT, et al (2012). Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). *Ann Oncol*, **23**, 1880-8.
- Fuchs CS, Colditz GA, Stampfer MJ, et al (1996). A prospective study of cigarette smoking and the risk of pancreatic cancer. *Arch Intern Med*, **156**, 2255-60.
- Hamajima N, Matsuo K, Saito T, et al (2001). Gene-environment interactions and polymorphism studies of cancer risk in the Hospital-based Epidemiologic Research Program at Aichi Cancer Center II (HERPACC-II). *Asian Pac J Cancer Prev*, **2**, 99-107.
- Heatherton TF, Kozlowski LT, Frecker RC, et al (1989). Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. *Bri J Addict*, **84**, 791-9.
- IARC (2004). Tobacco smoke and involuntary smoking. *IARC Monogr Eval Carcinog Risks Hum*, **83**, 519-56.
- Inoue M, Tajima K, Hirose K, et al (1997a). Epidemiological features of first-visit outpatients in Japan: comparison with general population and variation by sex, age, and season. *J Clin Epidemiol*, **50**, 69-77.
- Inoue M, Tajima K, Hirose K, et al (1997b). Epidemiological features of first-visit outpatients in Japan: comparison with general population and variation by sex, age, and season. *J Clin Epidemiol*, **50**, 69-77.
- Inoue M, Tajima K, Takezaki T, et al (2003). Epidemiology of pancreatic cancer in Japan: a nested case-control study from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC). *Int J Epidemiol*, **32**, 257-62.
- Kabat GC, Wynder EL (1987). Determinants of quitting smoking. *Am J Public Health*, **77**, 1301-5.
- Kanda J, Matsuo K, Suzuki T, et al (2009). Impact of alcohol consumption with polymorphisms in alcohol-metabolizing enzymes on pancreatic cancer risk in Japanese. *Cancer Sci*, **100**, 296-302.
- Kawase T, Matsuo K, Hiraki A, et al (2009). Interaction of the effects of alcohol drinking and polymorphisms in alcohol-metabolizing enzymes on the risk of female breast cancer in Japan. *J Epidemiol*, **19**, 244-50.
- Kozlowski LT, Porter CQ, Orleans CT, et al (1994). Predicting smoking cessation with self-reported measures of nicotine dependence: FTQ, FTND, and HSI. *Drug Alcohol Depend*, **34**, 211-6.
- Lee PN, Forey BA, Coombs KJ (2012). Systematic review with meta-analysis of the epidemiological evidence in the 1900s relating smoking to lung cancer. *BMC Cancer*, **12**, 385.
- Lin Y, Tamakoshi A, Kawamura T, et al (2002). A prospective cohort study of cigarette smoking and pancreatic cancer in

*Cigarette Smoking and Pancreatic Cancer Risk - no Association with the Nicotine-dependence Phenotype*

Japan. *Cancer Causes Control*, **13**, 249-54.

- Lin Y, Tamakoshi A, Kawamura T, et al (2001). An epidemiological overview of environmental and genetic risk factors of pancreatic cancer. *Asian Pac J Cancer Prev*, **2**, 271-80.
- Matsuo K, Gallus S, Negri E, et al (2012). Time to first cigarette and upper aero-digestive tract cancer risk in Japan. *Cancer Epidemiol Biomarkers Prev*, **21**, 1986-92.
- Matsuo K, Ito H, Wakai K, et al (2011). Cigarette smoking and pancreas cancer risk: an evaluation based on a systematic review of epidemiologic evidence in the Japanese population. *Jpn J Clin Oncol*, **41**, 1292-302.
- Muscat JE, Ahn K, Richie JP Jr, Stellman SD (2011a). Nicotine dependence phenotype and lung cancer risk. *Cancer*, **117**, 5370-6.
- Muscat JE, Ahn K, Richie JP Jr, Stellman SD (2011b). Nicotine dependence phenotype, time to first cigarette, and risk of head and neck cancer. *Cancer*, **117**, 5377-82.
- Muscat JE, Liu HP, Livelsberger C, et al (2012). The nicotine dependence phenotype, time to first cigarette, and larynx cancer risk. *Cancer Causes Control*, **23**, 497-503.
- Muscat JE, Stellman SD, Caraballo RS, Richie JP Jr (2009). Time to first cigarette after waking predicts cotinine levels. *Cancer Epidemiol Biomarkers Prev*, **18**, 3415-20.
- Muscat JE, Stellman SD, Hoffmann D, Wynder EL (1997). Smoking and pancreatic cancer in men and women. *Cancer Epidemiol Biomarkers Prev*, **6**, 15-9.
- Nilsen TI, Vatten LJ (2000). A prospective study of lifestyle factors and the risk of pancreatic cancer in Nord-Trondelag, Norway. *Cancer Causes Control*, **11**, 645-52.
- Partanen TJ, Vainio HU, Ojajarvi IA, Kauppinen TP (1997). Pancreas cancer, tobacco smoking and consumption of alcoholic beverages: a case-control study. *Cancer Lett*, **116**, 27-32.
- Pillitteri JL, Kozlowski LT, Sweeney CT, Heatherton TF (1997). Individual differences in the subjective effects of the first cigarette of the day: a self-report method for studying tolerance. *Exp Clin Psychopharmacol*, **5**, 83-90.
- Polesel J, Talamini R, La Vecchia C, et al (2008). Tobacco smoking and the risk of upper aero-digestive tract cancers: a reanalysis of case-control studies using spline models. *Int J Cancer*, **122**, 2398-402.
- Silverman DT, Dunn JA, Hoover RN, et al (1994). Cigarette smoking and pancreas cancer: a case-control study based on direct interviews. *J Natl Cancer Inst*, **86**, 1510-6.
- Suzuki T, Matsuo K, Hasegawa Y, et al (2008). Anthropometric factors at age 20 years and risk of thyroid cancer. *Cancer Causes Control*, **19**, 1233-42.
- Tajima K, Hirose K, Inoue M, et al (2000). A model of practical cancer prevention for out-patients visiting a hospital: the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC). *Asian Pac J Cancer Prev*, **1**, 35-47.
- Toll BA, Schepis TS, O'Malley SS, et al (2007). Subjective reactivity to the first cigarette of the day as a predictor of smoking relapse: a preliminary study. *Drug Alcohol Depend*, **89**, 302-5.