Research Article

Cancer Epidemiology, Biomarkers & Prevention

# Smoking and Pancreatic Cancer Incidence: A Pooled Analysis of 10 Population-Based Cohort Studies in Japan

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## Abstract

**Background:** Detailed prospective evaluation of cigarette smoking associated with pancreatic cancer risk in large Asian populations is limited. The aim of this study was to examine this association in a Japanese population, with a particular focus on evaluating sex differences.

**Methods:** We performed a pooled analysis of 10 population-based cohort studies. We calculated study-specific HRs and 95% confidence intervals (CI) using Cox proportional hazards regression, and then estimated summary HRs by pooling these estimates with a random effects model.

**Results:** During 4,695,593 person-years of follow-up in 354,154 participants, 1,779 incident pancreatic cancer cases were identified. We observed an increased pancreatic cancer risk for current smoking compared with never smoking in both males [HR (95% CI), 1.59 (1.32–1.91)] and females [HR (95% CI), 1.81 (1.43–2.30)]. Significant risk elevations for former smoking and small cumulative dose of ≤20 pack-years (PY) were observed only among females, regardless of environmental tobacco smoke exposure. Trend analysis indicated significant 6% and nonsignificant 6% increases in pancreatic cancer risk for every 10 PYs in males and females, respectively. Risk became comparable with never smokers after 5 years of smoking cessation in males. In females, however, we observed no risk attenuation by smoking cessation.

**Conclusions:** This study supports the well-known association between smoking and pancreatic cancer and indicates potential sex differences in a Japanese population. Quitting smoking would be beneficial for pancreatic cancer prevention, especially in males.

**Impact:** Pancreatic cancer risk is increased with cumulative smoking exposure and decreased with smoking cessation, with potential sex differences.

## Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in developed countries (1). In Japan, pancreatic cancer was ranked the seventh most common cancer in 2014, with 36,156 new cases, and the fourth most frequent cause of cancer-related death in 2017, with 34,224 deaths (2). Because the early stages of pancreatic cancer do not usually produce symptoms and an early detection method has yet to be established, this cancer is generally diagnosed in the advanced stages, which contributes to a 5-year survival rate of only 7.7% (3). Identifying modifiable risk factors for the primary prevention of pancreatic cancer is therefore of the utmost importance.

The International Agency for Research on Cancer (IARC) concluded that smoking is one of the most important modifiable risk factors for pancreatic cancer (4). In a meta-analysis of 82 independent studies (42 case–control, 35 cohort, and five nested

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Cancer Epidemiol Biomarkers Prev 2019;28:1370–8

**doi:** 10.1158/1055-9965.EPI-18-1327

case–control studies) published between 1950 and 2007, the summary risks for current and former smokers relative to never smokers were 1.74 [95% confidence interval (CI), 1.61–1.87] and 1.20 (95% CI, 1.11–1.29), respectively (5). A second meta-analysis of 11 cohort studies published between 2000 and 2016 reported similar significant risk elevations of 66% for current smokers and 40% for former smokers (6). To date, a total of five prospective studies have evaluated the association between pancreatic cancer risk and smoking status using data from a Japanese population (7–12), all of which confirmed a significant risk elevation in current smokers in at least one sex. Furthermore, a recent meta-analysis of three case–control and four cohort studies in Japan reported a summary estimate for ever smoking of 1.68 (95% CI, 1.38–2.05; ref. 13), which is comparable with the results of meta- and pooled analyses (5, 6, 9, 11, 14, 15).

In addition to smoking status, studies have also evaluated the association of pancreatic cancer with the intensity and duration of cigarette smoking. Several meta- and pooled analyses have provided clear evidence that risk increases significantly with increasing daily cigarette consumption, duration of smoking, and pack-years (PY; refs. 5, 11, 14, 16). Moreover, risk in former smokers decreases to the same level as that in never smokers within 10–20 years of cessation (5, 14–16). These findings were mainly derived from Western populations, however, and prospective evidence on the association of pancreatic cancer incidence with the intensity and duration of smoking and years of smoking cessation from substantial Asian populations remains limited, especially among females. There have been three prospective studies (7, 8, 10, 12) evaluating the intensity and duration of smoking and two studies (7, 17) evaluating years of smoking cessation in Japanese populations, but detailed evaluations among females using the same categories as males were not conducted, mainly due to the small sample size of former or current smokers among females in Japan. Moreover, the relationship between pancreatic cancer risk and smoking considering sex differences has not been thoroughly investigated not only among Asian populations but also among Western populations, although many studies on lung cancer have suggested potential sex differences in susceptibility to the effects of smoking (18).

In this study, to examine the risk of pancreatic cancer incidence associated with cigarette smoking, including evaluation of cumulative smoking exposure and cessation, we pooled 10 population-based cohort studies in Japan, resulting in more than 350,000 participants. With this large population size, we evaluated all of the associations by sex using the equivalent categories between males and females, to evaluate potential sex differences in particular.

## Materials and Methods

### Study population

The study population was collected from large-scale population-based cohort studies conducted in Japan. Inclusion criteria for this study have been described elsewhere (17). Ten studies met the criteria and were included in this study, namely the Japan Public Health Center-based Prospective Study (JPHC-I and -II; ref. 19), the Japan Collaborative Cohort Study (JACC; ref. 20), the Miyagi Cohort Study (MIYAGI-I; ref. 21), the Three-Prefecture Cohort Study in Miyagi (MIYAGI-II; ref. 22), the Three-Prefecture Cohort Study in Aichi (AICHI; ref. 22), the Takayama Study (TAKAYAMA; ref. 10), the Ohsaki Cohort Study (OHSAKI; ref. 23), the Three-Prefecture Cohort Study in Osaka (OSAKA; ref. 22), and the Life Span Study (LSS; ref. 24; Table 1). Participants with a past history of cancer at baseline, those without information on smoking, and those with estimated radiation doses from the atomic bombing of $\geq$100 mGy (for LSS) were excluded from the analyses. Each study was reviewed and approved by its relevant institutional ethics review board.

Four studies (JPHC-I and -II, JACC, and TAKAYAMA) have already published results on the association of smoking with pancreatic cancer risk in their respective cohorts (7, 8, 10, 12). We reanalyzed the results of each study using the updated dataset in this study.

### Assessment of exposure

In each study, smoking status, cumulative smoking exposure, and years of smoking cessation were assessed using a self-administered questionnaire at baseline. For smoking status, subjects were categorized into three groups, including never smokers, former smokers, and current smokers. Cumulative smoking exposure was evaluated by PYs, defined as the number of packs smoked per day (or the number of cigarettes smoked per day divided by 20) multiplied by the number of years of smoking. Subjects were then classified into five groups for males: 0 (never smokers), >0–20, >20–40, >40–60, and >60; and four groups for females: 0, >0–20, >20–40, and >40. Subjects were then additionally classified into five groups by smoking status: never smokers, former smokers, and current smokers with >0–20, >20–40, or >40 PYs. To evaluate the impact of smoking cessation, subjects were classified into five groups: never smokers, former smokers with $\geq$10, 5–9, or 0–4 years of smoking cessation, and current smokers. Important covariates for pancreatic cancer, including body mass index (BMI), alcohol consumption, history of diabetes, and environmental tobacco smoke (ETS) exposure were also collected via a self-administered questionnaire. BMI was calculated as weight in kilograms divided by the square of the height in meters using information obtained in the questionnaire.

### Follow-up and assessment of outcome

As shown in Table 1, participants were followed-up from the time of baseline survey (JPHC-I: 1990, JPHC-II: 1993, JACC: 1988, MIYAGI-I: 1990, Miyagi-II: 1984, AICHI: 1985, TAKAYAMA: 1992, OHSAKI: 1994, OSAKA: 1983, and LSS: 1991) until the last date of follow-up in each study (JPHC-I and -II: 2010, JACC: 2009, MIYAGI-I: 2007, MIYAGI-II: 1992, AICHI: 2000, TAKAYAMA: 2008, OHSAKI: 2005, OSAKA: 2000, and LSS: 2003). We confirmed residential status, including survival, date of death, and date of moving out of the study area through the residential registries maintained by the municipal governments of the study areas. Pancreatic cancer cases were identified via local cancer registries or direct access to major local hospitals. Information on cancer diagnosis was gathered for the whole population and coded using the International Classification of Diseases for Oncology, third edition (ICD-O-3; ref. 25), the ICD, ninth revision (ICD-9; ref. 26), or ICD, 10th revision (ICD-10; ref. 27). Study outcome was defined as pancreatic cancer incidence (ICD-9: 157.0–157.9, ICD-10 or ICD-O-3: C25.0–C25.9) during the follow-up period of the respective study.

### Statistical analysis

Person-years of follow-up were calculated from the date of the baseline survey until the date of death, loss to follow-up

**Table 1.** Characteristics of the cohort studies in this pooled analysis of 10 population-based cohort studies in Japan

| Study | Initial population | Age range at baseline, years | Follow-up (start–end) | Average follow-up period, years | Number of subjects | | Number of cases | | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Men | Women | Men | Women | |
| JPHC-I | Japanese residents of five public health center areas in Japan | 40–59 | 1990–2010 | 18.6 | 19,676 | 21,628 | 141 | 108 | Subjects of one public health center area were excluded due to lack of incidence data. |
| JPHC-II | Japanese residents of six public health center areas in Japan | 40–69 | 1993–2010 | 15.6 | 23,305 | 26,216 | 139 | 138 | |
| JACC | Residents from 45 areas throughout Japan | 40–79 | 1988–2009 | 12.9 | 24,727 | 33,769 | 185 | 199 | A total of 22 selected areas with cancer incidence follow-up data were used in this analysis. |
| MIYAGI-I | Residents of 14 municipalities in Miyagi Prefecture, Japan | 40–64 | 1990–2007 | 15.7 | 19,373 | 17,291 | 119 | 64 | |
| MIYAGI-II | Residents of three municipalities in Miyagi Prefecture, Japan | 40+ | 1984–1992 | 7.6 | 9,877 | 11,537 | 24 | 25 | |
| AICHI | Residents of two municipalities in Aichi Prefecture, Japan | 40–103 | 1985–2000 | 11.5 | 15,416 | 15,574 | 69 | 53 | |
| TAKAYAMA | Residents of Takayama City, Gifu Prefecture, Japan | 35–101 | 1992–2008 | 13.6 | 13,832 | 14,832 | 80 | 59 | |
| OHSAKI | Residents of 14 municipalities in Miyagi Prefecture, Japan | 40–79 | 1994–2005 | 9.0 | 19,177 | 18,748 | 79 | 74 | |
| OSAKA | Residents of four municipalities in Osaka Prefecture, Japan | 40–97 | 1983–2000 | 12.2 | 15,559 | 16,628 | 99 | 55 | |
| LSS | Atomic bomb survivors in Hiroshima and Nagasaki, Japan | 46–104 | 1991–2003 | 10.8 | 5,978 | 11,011 | 26 | 43 | LSS originally started in 1950. This analysis included subjects who responded to the 1991 survey. |
| Total | | | | | 166,920 | 187,234 | 961 | 818 | |

(emigration from the study area), diagnosis of pancreatic cancer, or end of follow-up, whichever occurred first. Study-specific analyses were performed to allow pooling in the estimation of summary statistics. In each study, we estimated the HRs and their two-sided 95% CIs for the incidence of pancreatic cancer associated with smoking status, cumulative smoking exposure, and years of smoking cessation, respectively, using a Cox proportional hazards model. Never smokers were defined as the reference category in all analyses. All studies estimated two types of HR: model 1, with adjustment for age at baseline (and area for multicentric studies, namely JPHC-I, JPHC-II, JACC, and LSS); and model 2, with the same adjustment as model 1 and additionally with adjustment for well-known risk factors for pancreatic cancer, namely BMI (<23, 23–<25, and $\geq$25 kg/m$^2$), alcohol consumption [males: nondrinker, occasional drinker (less than once a week), and current drinker (<23, 23–<46, 46–<69, and $\geq$69 ethanol g/day); and females: nondrinker, occasional drinker, and current drinker (<23 and $\geq$23 ethanol g/day)], and history of diabetes (yes or no). Furthermore, we estimated HRs with the same adjustment as model 2 and additionally with adjustment for ETS exposure (model 3). Eight of 10 studies, namely JPHC-I, JPHC-II, JACC, MIYAGI-I, Miyagi-II, AICHI, OHSAKI, and OSAKA, collected information on ETS. Because the questionnaires were not detailed and were not homogeneous across the studies, we created two variables using broad ETS exposure categories as follows: ETS during childhood (yes or no) and ETS at home and/or at work (yes or no). HRs of years after smoking cessation were estimated with additional adjustment for PYs (continuous; models 4 and 5). Among covariates, there were 6.6% missing data for BMI ($n$ = 23,254), 3.6% for alcohol consumption ($n$ = 12,852), 12.9% for history of diabetes ($n$ = 45,692), 5.9% for ETS during childhood ($n$ = 18,169), and 9.6% for ETS at home and/or at work ($n$ = 29,606). Missing data of each covariate was coded as an indicator term. We also estimated HRs with exclusion of cases diagnosed within 3 years of baseline. With the same covariate adjustment, we performed trend analyses for PYs (unit HRs per 10 PYs) and years of smoking cessation (unit HRs per 1 year) by excluding never smokers (PYs = 0) and current smokers (years of smoking cessation = 0), respectively. Moreover, to investigate whether the effect of cigarette smoking was homogeneous within strata of ETS exposure, we conducted analyses stratified by ETS exposure.

Study-specific results were then pooled using a random effects model (28). We evaluated the extent of heterogeneity for each category by Cochran $Q$-statistic, which we considered as statistically significant when $P < 0.10$. We also reported the $I^2$ statistic to describe the percentage of total variation in the study-specific HRs, which was due to between-study heterogeneity (29). $P$ values for the interaction between cigarette smoking and sex were obtained using meta-regression analysis. The assumption of proportional hazards was evaluated graphically using a log-negative-log plot and no major violations of the proportional hazards assumption were detected. Analyses were performed with SAS version 9.4 (SAS Institute, Inc.) or STATA version 15.1 (Stata Corporation). We interpreted two-sided $P < 0.05$ as statistically significant.

In addition, to assess the impact of smoking on the risk of pancreatic cancer, the population attributable fraction (PAF) (%) was estimated as

$$\frac{A1}{M1} \times \frac{HR-1}{HR}$$

where $A1$ represents the number of exposed cases and $M1$ represents the number of total cases (30, 31). The 95% CI of PAF was estimated using the variance of ln(1−PAF):

$$\mathrm{Var}[\ln(1-\mathrm{PAF})] = \frac{PAF^2}{(1-PAF)^2}\left[\frac{V}{(HR-1)^2} + \frac{2}{A1\times(HR-1)} + \frac{A0}{A1\times M1}\right]$$

where V is the variance of ln(HR) and $A0$ represents the number of unexposed cases, and the interval estimate of PAF was obtained by $1-\exp[\ln(1-\mathrm{PAF}) \pm 1.96\sqrt{Var[\ln(1-\mathrm{PAF})]}]$ (31).

## Results

This study included 10 cohort studies comprising 354,154 subjects (166,920 males and 187,234 females) with 4,695,593 person-years of follow-up (average follow-up: 12.7 years). In total, 1,779 incident pancreatic cancer cases (961 males and 818 females) were identified (Table 1).

On comparison of former and current smokers with never smokers (Supplementary Table S1), statistically significant associations were observed among female former smokers [adjusted (model 2) HR (aHR), 1.77; 95% CI, 1.19–2.62] and current smokers (males, aHR = 1.59; 95% CI, 1.32–1.91; females, aHR = 1.81, 95% CI, 1.43–2.30). In contrast, no significant association was observed among male former smokers (aHR 1.10; 95% CI, 0.89–1.36). Pooled results for cumulative smoking exposure among ever smokers compared with never smokers are presented in Table 2. In males, aHRs (95% CIs) for those with >0–20, >20–40, >40–60, and >60 PYs were 1.15 (0.92–1.44), 1.44 (1.19–1.75), 1.62 (1.30–2.02), and 1.71 (1.16–2.51), respectively. In females, aHRs (95% CIs) for those with >0–20, >20–40, and >40 PYs were 1.65 (1.28–2.13), 2.40 (1.65–3.49), and 1.90 (0.78–4.65), respectively. Trend analysis suggested that higher cumulative smoking exposure was significantly associated with increased pancreatic cancer risk in males (per 10 PYs: aHR, 1.06; 95% CI, 1.03–1.10) and was nonsignificantly associated in females (per 10 PYs: aHR, 1.06; 95% CI, 0.92–1.22). Pooled results for cumulative smoking exposure among current smokers are presented in Table 3. In males, statistically significant risk elevation was observed in all exposure categories compared with never smokers (>0–20 PYs: aHR = 1.39, 95% CI, 1.06–1.83; >20–40 PYs: aHR = 1.56, 95% CI, 1.27–1.91; and >40 PYs: aHR = 1.80, 95% CI, 1.46–2.24). Similarly, statistically significant risk elevation was observed in all exposure categories except in the highest category in females (>0–20 PYs: aHR = 1.67, 95% CI, 1.23–2.25;

**Table 2.** HRs and 95% CIs for pancreatic cancer risk according to cumulative smoking exposure

| | Cumulative smoking exposure by PYs | | | | | |
|---|---|---|---|---|---|---|
| | **0** | **>0–20** | **>20–40** | **>40–60** | **>60** | **Trend (per 10 PYs)** |
| Males | | | | | | |
| Number of subjects (*N*) | 34,767 | 38,187 | 56,791 | 25,219 | 9,596 | |
| Person-years (*N*) | 472,219 | 507,495 | 741,730 | 307,084 | 113,838 | |
| Number of cases (*N*) | 157 | 183 | 335 | 188 | 75 | |
| Crude rate (per 100,000) | 33.2 | 36.1 | 45.2 | 61.2 | 65.9 | |
| HR (Model 1) overall | 1.00 (ref) | 1.20 (0.97–1.49) | **1.48 (1.22–1.80)** | **1.67 (1.35–2.08)** | **1.74 (1.19–2.54)** | **1.06 (1.03–1.10)** |
| HR (Model 2) overall | 1.00 (ref) | 1.15 (0.92–1.44) | **1.44 (1.19–1.75)** | **1.62 (1.30–2.02)** | **1.71 (1.16–2.51)** | **1.06 (1.03–1.10)** |
| HR (Model 3) overall | 1.00 (ref) | 1.15 (0.90–1.47) | **1.51 (1.22–1.87)** | **1.65 (1.30–2.10)** | **1.66 (1.11–2.46)** | **1.06 (1.02–1.10)** |
| HR (Model 1) excluding early cases | 1.00 (ref) | 1.17 (0.92–1.48) | **1.50 (1.22–1.84)** | **1.65 (1.29–2.10)** | **1.60 (1.14–2.24)** | **1.06 (1.02–1.10)** |
| HR (Model 2) excluding early cases | 1.00 (ref) | 1.13 (0.88–1.44) | **1.46 (1.18–1.80)** | **1.62 (1.27–2.06)** | **1.53 (1.10–2.15)** | **1.06 (1.03–1.10)** |
| HR (Model 3) excluding early cases | 1.00 (ref) | 1.12 (0.86–1.46) | **1.53 (1.22–1.93)** | **1.65 (1.23–2.22)** | **1.49 (1.04–2.14)** | **1.05 (1.01–1.10)** |
| | **0** | **>0–20** | **>20–40** | **>40** | | **Trend (per 10 PYs)** |
| Females | | | | | | |
| Number of subjects (*N*) | 167,918 | 13,685 | 4,124 | 968 | | |
| Person-years (*N*) | 228,7817 | 172,628 | 46,914 | 10,630 | | |
| Number of cases (*N*) | 703 | 75 | 31 | 5 | | |
| Crude rate (per 100,000) | 30.7 | 43.4 | 66.1 | 47.0 | | |
| HR (Model 1) overall | 1.00 (ref) | **1.80 (1.42–2.30)** | **2.42 (1.68–3.48)** | 2.06 (0.86–4.99) | | 1.05 (0.92–1.20) |
| HR (Model 2) overall | 1.00 (ref) | **1.65 (1.28–2.13)** | **2.40 (1.65–3.49)** | 1.90 (0.78–4.65) | | 1.06 (0.92–1.22) |
| HR (Model 3) overall | 1.00 (ref) | **1.60 (1.20–2.14)** | **2.25 (1.48–3.43)** | 1.91 (0.78–4.66) | | 1.09 (0.93–1.28) |
| HR (Model 1) excluding early cases | 1.00 (ref) | **1.75 (1.34–2.28)** | **2.45 (1.65–3.64)** | **2.51 (1.03–6.09)** | | 1.08 (0.94–1.24) |
| HR (Model 2) excluding early cases | 1.00 (ref) | **1.60 (1.22–2.11)** | **2.37 (1.57–3.57)** | 2.35 (0.96–5.77) | | 1.09 (0.94–1.26) |
| HR (Model 3) excluding early cases | 1.00 (ref) | **1.56 (1.14–2.13)** | **2.37 (1.51–3.72)** | 2.39 (0.97–5.86) | | 1.15 (0.97–1.35) |

NOTE: Model 1 was adjusted for age and area (for multicentric studies, namely JPHC-I, JPHC-II, JACC, and LSS); model 2 was adjusted for age, area, BMI (<23, 23–<25, and ≥25 kg/m$^2$), alcohol consumption [men: nondrinker, occasional drinker (less than once a week), and current drinker (<23, 23–<46, 46–<69, and ≥69 ethanol g/day); women: nondrinker, occasional drinker and current drinker (<23 and ≥23 ethanol g/day)], and history of diabetes; model 3 was adjusted for age, area, BMI (<23, 23–<25, and ≥25 kg/m$^2$), alcohol consumption [men: nondrinker, occasional drinker (less than once a week), and current drinker (<23, 23–<46, 46–<69, and ≥69 ethanol g/day); women: nondrinker, occasional drinker, and current drinker (<23 and ≥23 ethanol g/day)], history of diabetes, ETS during childhood, and ETS at home and/or at work. We excluded TAKAYAMA and LSS in which no information on ETS was available; for the trend analysis, never smokers (PY = 0) were excluded. Between-study heterogeneity for the risk estimate by the trend analysis was evaluated using the *Q*-statistic and $I^2$-statistic. *Q*-statistic was considered as statistically significant when $P < 0.10$; 0% of $I^2$-statistic represented no heterogeneity. *Q*-statistics were not statistically significant in all risk estimates. $I^2$-statistics were 0% in all risk estimates except the estimate in males obtained by model 1 (excluding early cases; $I^2$-statistic = 4.7%); HR values in bold show statistical significance ($P < 0.05$); a pooled analysis of 10 population-based cohort studies in Japan.

**Table 3.** HRs and 95% CIs for pancreatic cancer risk according to smoking status considering cumulative smoking exposure among current smokers

| | Smoking status considering cumulative smoking exposure among current smokers | | | | |
|---|---|---|---|---|---|
| | | | Current (cumulative smoking exposure by PYs) | | |
| | **Never** | **Former** | **>0–20** | **>20–40** | **>40** |
| Males | | | | | |
| Number of subjects (*N*) | 34,767 | 40,046 | 18,864 | 45,169 | 27,394 |
| Person-years (*N*) | 472,219 | 505,672 | 254,956 | 595,254 | 333,988 |
| Number of cases (*N*) | 157 | 223 | 89 | 267 | 222 |
| Crude rate (per 100,000) | 33.2 | 44.1 | 34.9 | 44.9 | 66.5 |
| HR (Model 1) overall | 1.00 (ref) | 1.14 (0.92–1.41) | **1.42 (1.08–1.86)** | **1.59 (1.30–1.95)** | **1.84 (1.49–2.27)** |
| HR (Model 2) overall | 1.00 (ref) | 1.10 (0.89–1.37) | **1.39 (1.06–1.83)** | **1.56 (1.27–1.91)** | **1.80 (1.46–2.24)** |
| HR (Model 3) overall | 1.00 (ref) | 1.13 (0.89–1.42) | **1.40 (1.04–1.90)** | **1.63 (1.31–2.04)** | **1.85 (1.47–2.35)** |
| HR (Model 1) excluding early cases | 1.00 (ref) | 1.11 (0.88–1.39) | **1.36 (1.01–1.83)** | **1.60 (1.29–1.99)** | **1.80 (1.43–2.26)** |
| HR (Model 2) excluding early cases | 1.00 (ref) | 1.07 (0.84–1.35) | **1.35 (1.00–1.83)** | **1.57 (1.26–1.96)** | **1.79 (1.41–2.26)** |
| HR (Model 3) excluding early cases | 1.00 (ref) | 1.08 (0.84–1.39) | 1.35 (0.97–1.86) | **1.65 (1.30–2.10)** | **1.85 (1.37–2.50)** |
| Females | | | | | |
| Number of subjects (*N*) | 167,918 | 4,466 | 10,183 | 3,645 | 816 |
| Person-years (*N*) | 2,28,7817 | 51,938 | 131,007 | 41,865 | 9,102 |
| Number of cases (*N*) | 703 | 28 | 53 | 28 | 5 |
| Crude rate (per 100,000) | 30.7 | 53.9 | 40.5 | 66.9 | 54.9 |
| HR (Model 1) overall | 1.00 (ref) | **1.86 (1.27–2.73)** | **1.86 (1.40–2.47)** | **2.58 (1.77–3.78)** | **2.47 (1.02–5.98)** |
| HR (Model 2) overall | 1.00 (ref) | **1.77 (1.19–2.62)** | **1.67 (1.23–2.25)** | **2.60 (1.75–3.84)** | 2.31 (0.94–5.64) |
| HR (Model 3) overall | 1.00 (ref) | **1.91 (1.23–2.96)** | **1.63 (1.16–2.29)** | **2.36 (1.51–3.69)** | 2.29 (0.94–5.59) |
| HR (Model 1) excluding early cases | 1.00 (ref) | **1.82 (1.17–2.83)** | **1.86 (1.37–2.53)** | **2.54 (1.67–3.86)** | **2.99 (1.23–7.25)** |
| HR (Model 2) excluding early cases | 1.00 (ref) | **1.80 (1.15–2.82)** | **1.67 (1.21–2.30)** | **2.48 (1.61–3.831)** | **2.84 (1.16–6.96)** |
| HR (Model 3) excluding early cases | 1.00 (ref) | **1.99 (1.23–3.23)** | **1.58 (1.10–2.28)** | **2.43 (1.50–3.93)** | **2.87 (1.17–7.04)** |

NOTE: Model 1 was adjusted for age and area (for multicentric studies, namely JPHC-I, JPHC-II, JACC, and LSS); model 2 was adjusted for age, area, BMI (<23, 23–<25, and ≥25 kg/m$^2$), alcohol consumption [men: nondrinker, occasional drinker (less than once a week), and current drinker (<23, 23–<46, 46–<69, and ≥69 ethanol g/day); women: nondrinker, occasional drinker, and current drinker (<23 and ≥23 ethanol g/day)], and history of diabetes; model 3 was adjusted for age, area, BMI (< 23, 23–<25, and ≥25 kg/m$^2$), alcohol consumption [men: nondrinker, occasional drinker (less than once a week), and current drinker (<23, 23–<46, 46–<69, and ≥69 ethanol g/day); women: nondrinker, occasional drinker, and current drinker (<23 and ≥23 ethanol g/day)], history of diabetes, ETS during childhood, and ETS at home and/or at work. We excluded TAKAYAMA and LSS in which no information on ETS was available; HR values in bold show statistical significance ($P < 0.05$). Between-study heterogeneity was evaluated using the *Q*-statistic and $I^2$-statistic. *Q*-statistic was considered as statistically significant when $P < 0.10$; 0% of $I^2$-statistic represented no heterogeneity. *Q*-statistics were not statistically significant in all risk estimates. $I^2$-statistics were 0% in all risk estimates except those for male former smoking (model 1, 1.9%; model 3, 0.7%) and male current smoking with >40 PYs (model 3 excluding early cases, 24.1%). A pooled analysis of 10 population-based cohort studies in Japan.

>20–40 PYs: aHR = 2.60, 95% CI, 1.75–3.84; and >40 PYs: aHR = 2.31, 95% CI, 0.94–5.64). In terms of years after smoking cessation in males, the risk of former smokers with ≥5 years after quitting smoking did not differ from that of never smokers, although the result of the trend analysis was nonsignificant (Table 4). In contrast, we observed no risk attenuation by smoking cessation in females. Even after ≥10 years of smoking cessation, the risk of pancreatic cancer was still significant in females, although the point estimates declined with increasing years since smoking cessation in the categorical evaluation.

Results remained largely unchanged following the additional adjustment for ETS exposure and the exclusion of cases diagnosed early within 3 years after enrollment. The associations of smoking status (never, former, and current) and cumulative smoking exposure (0, >0–20, and >20) with pancreatic cancer risk were further assessed in analyses stratified by ETS during childhood and ETS at home and/or at work (Supplementary Tables S2 and S3). The association seemed stronger in participants without ETS during childhood and in participants without ETS at home and/or at work, but significant risk elevations among former smokers and ever smokers with ≤20 PYs were observed across all strata of ETS exposure only in females. In all analyses, we found no significant heterogeneity across studies. Regarding sex differences, we observed significant interactions of sex with former smoking ($P = 0.039$) and small cumulative dose (≤20 PYs; $P = 0.034$).

Finally, we calculated PAF of former and current smoking on pancreatic cancer incidence. For males, PAF estimates (95% CI) were 2.11% (−2.65–6.64) for former smokers and 22.4% (14.1–30.0) for current smokers. For females, PAF estimates were 1.49% (0.19–2.77) for former smokers and 4.76% (2.43–7.03) for current smokers.

## Discussion

In this study, we conducted a pooled analysis using data from 10 population-based cohort studies comprising a total of 354,154 Japanese subjects. With 1,779 incident pancreatic cancer cases, this prospective analysis is one of the largest to date in an Asian country. Compared with never smokers, male and female current smokers showed a significantly increased risk of pancreatic cancer incidence of 59% and 81%, respectively. For former smokers, females showed a significantly increased risk of 77% relative to never smokers, whereas no significant association was seen in males. With respect to cumulative smoking exposure, significant and nonsignificant dose–response associations with increasing PYs were observed in males and females, respectively (males: aHR of per 10 PY 1.06, 95% CI, 1.03–1.10; females: aHR of per 10 PY 1.06, 95% CI, 0.92–1.22). In terms of smoking cessation, risk became comparable with never smokers after 5 years of smoking cessation in males. In contrast, no such association was seen in females.

Our results suggest the possibility of sex differences in pancreatic cancer risk associated with smoking. Although we observed a consistently increased pancreatic cancer risk for current smoking

**Table 4.** HRs and 95% CIs for pancreatic cancer risk according to years of smoking cessation

| | Smoking status considering years of smoking cessation among former smokers | | | | | |
|---|---|---|---|---|---|---|
| | | Former (years of smoking cessation) | | | | |
| | Never | ≥10 | 5–9 | 0–4 | Current | Trend (per 1 year) |
| Males | | | | | | |
| Number of subjects (*N*) | 34,767 | 19,064 | 9,511 | 11,189 | 92,107 | |
| Person-years (*N*) | 472,219 | 240,354 | 122,310 | 139,877 | 1,193,243 | |
| Number of cases (*N*) | 157 | 109 | 38 | 72 | 581 | |
| Crude rate (per 100,000) | 33.2 | 45.3 | 31.1 | 51.5 | 48.7 | |
| HR (Model 1) overall | 1.00 (ref) | 1.09 (0.85–1.41) | 1.00 (0.60–1.66) | **1.55 (1.16–2.06)** | **1.62 (1.36–1.94)** | 0.99 (0.98–1.01) |
| HR (Model 4) overall | 1.00 (ref) | 1.01 (0.77–1.32) | 0.90 (0.61–1.34) | 1.29 (0.93–1.78) | **1.50 (1.21–1.86)** | 0.99 (0.97–1.01) |
| HR (Model 5) overall | 1.00 (ref) | 0.98 (0.72–1.33) | 0.88 (0.56–1.37) | 1.39 (0.98–1.97) | **1.53 (1.19–1.95)** | 0.98 (0.96–1.01) |
| HR (Model 1) excluding early cases | 1.00 (ref) | 1.02 (0.77–1.35) | 0.94 (0.63–1.41) | **1.63 (1.19–2.23)** | **1.61 (1.32–1.95)** | 0.99 (0.98–1.01) |
| HR (Model 4) excluding early cases | 1.00 (ref) | 0.97 (0.72–1.31) | 0.94 (0.62–1.42) | **1.45 (1.02–2.06)** | **1.55 (1.23–1.95)** | 0.99 (0.97–1.01) |
| HR (Model 5) excluding early cases | 1.00 (ref) | 0.93 (0.67–1.30) | 0.82 (0.51–1.30) | **1.49 (1.02–2.17)** | **1.50 (1.15–1.95)** | 0.99 (0.97–1.01) |
| Females | | | | | | |
| Number of subjects (*N*) | 167,918 | 1,798 | 999 | 1,575 | 14,850 | |
| Person-years (*N*) | 2,287,817 | 20,531 | 11,685 | 18,587 | 184,705 | |
| Number of cases (*N*) | 703 | 13 | 7 | 7 | 87 | |
| Crude rate (per 100,000) | 30.7 | 63.3 | 59.9 | 37.7 | 47.1 | |
| HR (Model 1) overall | 1.00 (ref) | **2.35 (1.35–4.07)** | **3.41 (1.61–7.23)** | **3.81 (1.78–8.14)** | **1.94 (1.55–2.43)** | 1.01 (0.97–1.05) |
| HR (Model 4) overall | 1.00 (ref) | **1.93 (1.03–3.63)** | **3.36 (1.53–7.39)** | **3.93 (1.66–9.31)** | **1.86 (1.34–2.58)** | 1.01 (0.96–1.06) |
| HR (Model 5) overall | 1.00 (ref) | **2.17 (1.07–4.41)** | **3.36 (1.32–8.56)** | **4.04 (1.70–9.60)** | **1.82 (1.27–2.61)** | 1.00 (0.92–1.07) |
| HR (Model 1) excluding early cases | 1.00 (ref) | **2.18 (1.12–4.22)** | **4.18 (1.72–10.16)** | **3.99 (1.76–9.05)** | **1.95 (1.53–2.49)** | 1.01 (0.97–1.06) |
| HR (Model 4) excluding early cases | 1.00 (ref) | **2.05 (0.99–4.26)** | **3.96 (1.54–10.16)** | **3.76 (1.51–9.37)** | **1.92 (1.36–2.72)** | 1.01 (0.95–1.07) |
| HR (Model 5) excluding early cases | 1.00 (ref) | 2.29 (0.98–5.37) | **3.92 (1.53–10.09)** | **3.88 (1.55–9.71)** | **1.81 (1.24–2.65)** | 0.99 (0.90–1.08) |

NOTE: Model 1 was adjusted for age and area (for multicentric studies, namely JPHC-I, JPHC-II, JACC, and LSS); model 4 was adjusted for age, area, BMI (<23, 23–<25, and ≥25 kg/m$^2$), alcohol consumption [men: nondrinker, occasional drinker (less than once a week), and current drinker (<23, 23–<46, 46–<69, and ≥69 ethanol g/day); women: nondrinker, occasional drinker, and current drinker (<23 and ≥23 ethanol g/day)], history of diabetes, and PYs (continuous); model 5 was adjusted for age, area, BMI (< 23, 23–<25, and ≥25 kg/m$^2$), alcohol consumption [men: nondrinker, occasional drinker (less than once a week), and current drinker (<23, 23–<46, 46–<69, and ≥69 ethanol g/day); women: nondrinker, occasional drinker, and current drinker (<23 and ≥23 ethanol g/day)], history of diabetes, PYs (continuous), ETS during childhood, and ETS at home and/or at work. We excluded TAKAYAMA and LSS in which no information on ETS was available. For the trend analysis, current smokers (years of smoking cessation = 0) were excluded. Between-study heterogeneity for the risk estimate by the trend analysis was evaluated using the *Q*-statistic and $I^2$-statistic. *Q*-statistic was considered as statistically significant when $P < 0.10$; 0% of $I^2$-statistic represented no heterogeneity. In all risk estimates, *Q*-statistics were not statistically significant and $I^2$-statistics were 0%; HR values in bold show statistical significance ($P < 0.05$). A pooled analysis of 10 population-based cohort studies in Japan.

in both sexes, significant risk elevations among former smokers and ever smokers with ≤20 PYs were observed only in females (Supplementary Tables S1 and S2). In addition, the beneficial effect of smoking cessation in relation to pancreatic cancer risk appears to be more apparent in males than females (Table 4). Additional adjustment for ETS exposure and analyses stratified by ETS exposure (Supplementary Tables S2 and S3) did not change our results substantially, suggesting that females might be more susceptible to the effects of smoking than males regardless of exposure to ETS. *P* values for interaction by sex also supported the possibility of sex differences. In contrast, most previous meta- and pooled analyses mainly reported sex-combined results (5, 6, 11, 14, 16), and three of these found no significant interaction of sex with smoking (11, 14, 16). In addition, a review by the IARC based on six epidemiologic studies reported that the effect of sex on pancreatic cancer associated with smoking was comparable between males and females (4). However, a prospective cohort study in Sweden which evaluated the associations of smoking habits with pancreatic cancer incidence by sex showed that occasional and passive smoking were significant risk factors only in females, suggesting potential sex differences (18). Two prospective studies conducted in Japan also showed the possibility of sex differences (9, 12). The first of these studies evaluated the association between death from tobacco-related cancers and smoking status. Results showed that former smoking was significantly associated with risk of pancreatic cancer only in females. In contrast, for most of the other tobacco-related cancers, consistent increased risk in former smoking was observed in both sexes (9). The second study showed a significantly increased risk of pancreatic cancer death associated with low intensity (<20 cigarettes/day), short duration (<20 years), and small cumulative dose (<20 PYs) only in females (12). Many studies on lung cancer have suggested that women might be more susceptible to the effects of smoking than men, although this remains controversial (32–34). With regard to pancreatic cancer, however, these putative sex differences have not been thoroughly investigated (18).

One hypothesis that may explain the sex differences is anti-estrogenic effects of smoking (35). In laboratory settings, estrogen inhibited the development and growth of preneoplastic lesions of the pancreas (36) and the growth of transplanted pancreatic carcinoma (37) in rat models. In epidemiologic settings, recent cohort studies demonstrated that the use of estrogen-only therapy was associated with a lower risk of pancreatic cancer, suggesting that increased estrogen exposure may reduce pancreatic cancer risk (38, 39). We therefore speculate that pancreatic cancer in females might be due not only to the carcinogenic components contained in cigarettes but also to the antiestrogenic effects of smoking. Differences in tobacco type used, smoking method, or factors related to internal dose may also explain the sex differences observed in this study. However, additional data on tobacco type used and factors related to internal dose were not available in any study, and information on smoking method was obtained in only four studies. We were therefore unable to evaluate these smoking aspects in this study. In the 1980s–2000s, when most of the

study data were collected, almost all tobacco was consumed as filtered manufactured cigarettes in Japan (ref. 40; http://www.pnlee.co.uk/Downloads/ISS/ISS-Japan_161220.pdf). Furthermore, one prospective study showed that there were no significant dose-dependent associations between the levels of tar and nicotine and the risk of pancreatic cancer (41). As for smoking method, although inhalation of cigarette smoke has been shown to be associated with the risk of lung cancer (42), a significant association of inhalation with the risk of pancreatic cancer has not been observed in previous studies (41, 43). Therefore, we consider that these aspects of smoking, tobacco type and smoking method, may not substantially explain the sex differences observed in this study. Nevertheless, studies evaluating these smoking aspects on the risk of pancreatic cancer considering sex differences are scarce, and further studies are needed. As for internal dose, sex differences in cigarette smoke metabolism were suggested in studies of chronic obstructive pulmonary disease and lung cancer (44). Future studies are warranted to explore this point. Alternatively, the sex differences due to smoking in this study might simply be due to chance, given the small prevalence of former or current smoking among females. Considering the strong impact of smoking on pancreatic cancer, however, further studies to investigate potential sex differences are warranted.

Regarding smoking cessation, the meta- and pooled analyses reported that a reduction in risk equivalent to the level of never smokers was observed after more than 10 years of cessation (5, 14–16). Similar to our previous findings (17), this study showed risk attenuation with smoking cessation in males, even with additional adjustment for PYs. Specifically, our study showed that risk of pancreatic cancer became comparable with that of never smokers after 5 years of smoking cessation in males. This finding is consistent with those of the European Prospective Investigation into Cancer and Nutrition study (43). Compared with the risk of lung cancer, in which it takes 15–20 years from smoking cessation to reach the same level of cancer risk as never smokers (17, 45), smoking cessation seems to be more beneficial in the risk of pancreatic cancer. Lynch and colleagues noted the possibility that smoking had a late-stage mechanistic effect in pancreatic carcinogenesis (16). Further exploration of the biologic effects of smoking on pancreatic cancer is warranted. With regard to females, however, our current results showed no risk attenuation by smoking cessation. This lack of benefit with cessation in females might be supported by estrogen's inhibitory role in early-stage pancreatic carcinogenesis and protective effects against tumor growth (36, 37). Moreover, some women may continue to be exposed to environmental cigarette smoking even after cessation, especially at home. Such exposure might obscure any beneficial effects of cessation, but further adjustment for ETS exposure (model 5) did not change the results remarkably. Nevertheless, because the point estimates declined with increasing years of smoking cessation in the categorical evaluation (Table 4), we consider that smoking cessation might be also beneficial in females.

It should also be mentioned that the magnitude of the effect of smoking on pancreatic cancer was equivalent to that observed in previous meta- and pooled analyses conducted overseas (5, 6, 11, 14, 15). This contrasts with the case of lung cancer, for which several epidemiologic studies have suggested that the effect magnitude of smoking is smaller in Japan than in other countries (46). Among several subtypes of lung cancer, a subtype with epidermal growth factor receptor (EGFR) mutation has been shown to have little association with smoking (47). The smaller effect of smoking on the relative risk of lung cancer in Japan has been therefore considered partially due to the high prevalence of this subtype among Japanese. Accordingly, unlike the case with lung cancer, which includes subtypes showing heterogeneity with respect to the carcinogenic effects of smoking, it is likely that pancreatic cancer does not include subtypes showing little or negative association with smoking. We consider that the equivalence in risk elevation in Japanese and other populations is partially due to the homogeneity of pancreatic cancer with respect to the carcinogenic effects of smoking.

This study has several strengths. First, it included a very large number of participants of overlapping birth generations collected from major large-scale prospective cohorts in Japan. This allowed us to have sufficient statistical power to estimate stable summary quantitative estimates of cigarette smoking among Japanese. Second, the categories for cumulative smoking exposure, years of smoking cessation, and covariates across studies were unified, removing the possibility of the heterogeneity that can occur in meta-analysis of published studies.

Several potential limitations also warrant mention. First, information on smoking was collected by self-administered questionnaire in all studies. Our findings might therefore have been affected by misclassification due to self-reporting errors. Second, because we conducted our analyses using only a baseline questionnaire, we were unable to account for any changes in exposure status of smoking or other covariates occurring after enrollment. Third, it is possible that some disease misclassification could have occurred in this study because not all cases of pancreatic cancer were histologically confirmed. Moreover, as this is an aggregation of cohort studies, we cannot perform analyses restricted to histologically confirmed cases because not all the included studies collected such data. However, a review of pancreatic cancer and smoking showed that the risk estimates of current and former cigarette smokers in studies with <80% of histologically confirmed cases did not considerably differ from those with ≥80% of histologically confirmed cases, and statistically significant associations with pancreatic cancer were retained (5). In addition, some prospective cohort studies of the association between smoking and the risk of pancreatic cancer have shown that excluding nonmicroscopically confirmed cases did not change the risk estimates appreciably (41, 43). Therefore, we consider that disease misclassification is unlikely to have changed our results substantially. Fourth, we did not consider competing risks in the analyses of this study. Therefore, the risk estimates might be underestimated because the participants who experience a competing event (i.e., death from smoking-related diseases other than pancreatic cancer) at a given time may have the same chance of developing pancreatic cancer after that time as the participants who continued in follow-up. Therefore, the potential benefits of smoking cessation observed in males should be interpreted with caution because the risk estimates considering competing risks could be higher. However, because the beneficial effects of smoking cessation on the risk of pancreatic cancer have been continuously observed by many previous studies, we consider that the risk estimates for smoking cessation are less biased. Fifth, we applied missing indicator method to handle missing data in this study. It is true that missing indicator method may lead to biased estimates (31). However, the results obtained with model 2 did not markedly differ from those obtained with model 1, suggesting

that these covariates did not have considerable impact on the association between smoking and pancreatic cancer risk. In addition, a review by IARC mentioned that adjusting for further potential confounders, including diabetes, BMI, alcohol, and dietary intake did not substantially influence the risk estimates for pancreatic cancer associated with cigarette smoking, judging from the results of previous large cohort studies (4). Therefore, we consider that applying the missing indicator method, a popular approach to dealing with missing data, may introduce only negligible bias in this study. Sixth, cancer cases were identified via local cancer registries or direct access to major local hospitals, and there might be unidentified cancer cases. However, the cancer registries, which were the main resource used to gather incidence information in all studies, use death certificates to record cancer cases in addition to incidence information by hospitals. Therefore, because pancreatic cancer has high case fatality, the number of incident pancreatic cancers missed by the registries would be small. Finally, although we considered important potential confounders in the analysis, the possibility of residual confounding remains.

In conclusion, our study is the largest prospective study in an Asian country to date to obtain an overall quantitative estimate of the association of cigarette smoking with pancreatic cancer incidence for both males and females. Our results confirm the well-known association between smoking status and pancreatic cancer, and additionally show that risk is increased with cumulative smoking exposure and decreased with smoking cessation. Furthermore, our study indicates potential sex differences in susceptibility to cigarette smoking. Considering that the respective fractions of pancreatic cancer incidence attributable to smoking are 25% and 6.2% in males and females, control of cigarette smoking should be considered an essential component of any primary prevention strategy for pancreatic cancer incidence in a Japanese population.

## Appendix

Research group members are listed at the following site (as of August 2018): http://epi.ncc.go.jp/en/can_prev/796/7955.html.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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## Acknowledgments

This study was supported by the National Cancer Center Research and Development Fund (30-A-15, 27-A-4), National Cancer Center, Tokyo, Japan.

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Received December 14, 2018; revised March 25, 2019; accepted May 16, 2019; published first May 21, 2019.

## References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al.; editors. GLOBOCAN 2012, estimated cancer incidence and mortality and prevalence worldwide in 2012 v1.0 IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013.
2. Cancer Registry and Statistics. Cancer information service, National Cancer Center, Japan. Available from: https://ganjoho.jp/reg_stat/statistics/dl/index.html. [in Japanese]
3. Matsuda T, Ajiki W, Marugame T, Ioka A, Tsukuma H, Sobue T, et al. Population-based survival of cancer patients diagnosed between 1993 and 1999 in Japan: a chronological and international comparative study. Jpn J Clin Oncol 2011;41:40–51.
4. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Personal habits and indoor combustions, Vol.100E. Lyon, France: International Agency for Research on Cancer; 2012.
5. Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. Langenbecks Arch Surg 2008;393:535–45.
6. Korc M, Jeon CY, Edderkaoui M, Pandol SJ, Petrov MS, Consortium for the Study of Chronic Pancreatitis, Diabetic, and Pancreatic Cancer (CPDPC). Tobacco and alcohol as risk factors for pancreatic cancer. Best Pract Res Clin Gastroenterol 2017;31:529–36.
7. Lin Y, Tamakoshi A, Kawamura T, Inaba Y, Kikuchi S, Motohashi Y, et al. A prospective cohort study of cigarette smoking and pancreatic cancer in Japan. Cancer Causes Control 2002;13:249–54.
8. Luo J, Iwasaki M, Inoue M, Sasazuki S, Otani T, Ye W, et al. Body mass index, physical activity and the risk of pancreatic cancer in relation to smoking status and history of diabetes: a large-scale population-based cohort study in Japan–the JPHC study. Cancer Causes Control 2007;18:603–12.
9. Katanoda K, Marugame T, Saika K, Satoh H, Tajima K, Suzuki T, et al. Population attributable fraction of mortality associated with tobacco smoking in Japan: a pooled analysis of three large-scale cohort studies. J Epidemiol 2008;18:251–64.
10. Nakamura K, Nagata C, Wada K, Tamai Y, Tsuji M, Takatsuka N, et al. Cigarette smoking and other lifestyle factors in relation to the risk of pancreatic cancer death: a prospective cohort study in Japan. Jpn J Clin Oncol 2011;41:225–31.
11. Ansary-Moghaddam A, Huxley R, Barzi F, Lawes C, Ohkubo T, Fang X, et al. The effect of modifiable risk factors on pancreatic cancer mortality in populations of the Asia-Pacific region. Cancer Epidemiol Biomarkers Prev 2006;15:2435–40.
12. Lin Y, Yagyu K, Ueda J, Kurosawa M, Tamakoshi A, Kikuchi S, et al. Active and passive smoking and risk of death from pancreatic cancer: findings from the Japan Collaborative Cohort Study. Pancreatology 2013;13:279–84.
13. Matsuo K, Ito H, Wakai K, Nagata C, Mizoue T, Tanaka K, et al. Cigarette smoking and pancreas cancer risk: an evaluation based on a systematic review of epidemiologic evidence in the Japanese population. Jpn J Clin Oncol 2011;41:1292–302.
14. Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Ann Oncol 2012;23:1880–8.
15. Ordonez-Mena JM, Schottker B, Mons U, Jenab M, Freisling H, Bueno-de-Mesquita B, et al. Quantification of the smoking-associated cancer risk with

rate advancement periods: meta-analysis of individual participant data from cohorts of the CHANCES consortium. BMC Med 2016;14:62.
16. Lynch SM, Vrieling A, Lubin JH, Kraft P, Mendelsohn JB, Hartge P, et al. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol 2009;170:403–13.
17. Saito E, Inoue M, Tsugane S, Ito H, Matsuo K, Wakai K, et al. Smoking cessation and subsequent risk of cancer: a pooled analysis of eight population-based cohort studies in Japan. Cancer Epidemiol 2017;51: 98–108.
18. Andersson G, Wennersten C, Borgquist S, Jirstrom K. Pancreatic cancer risk in relation to sex, lifestyle factors, and pre-diagnostic anthropometry in the Malmo Diet and Cancer Study. Biol Sex Differ 2016;7:66.
19. Tsugane S, Sobue T. Baseline survey of JPHC study–design and participation rate. Japan Public Health Center-based prospective study on cancer and cardiovascular diseases. J Epidemiol 2001;11:S24–9.
20. Tamakoshi A, Yoshimura T, Inaba Y, Ito Y, Watanabe Y, Fukuda K, et al. Profile of the JACC study. J Epidemiol 2005;15:S4–8.
21. Tsuji I, Nishino Y, Tsubono Y, Suzuki Y, Hozawa A, Nakaya N, et al. Follow-up and mortality profiles in the Miyagi Cohort Study. J Epidemiol 2004;14: S2–6.
22. Marugame T, Sobue T, Satoh H, Komatsu S, Nishino Y, Nakatsuka H, et al. Lung cancer death rates by smoking status: comparison of the Three-Prefecture Cohort study in Japan to the Cancer Prevention Study II in the USA. Cancer Sci 2005;96:120–6.
23. Tsuji I, Nishino Y, Ohkubo T, Kuwahara A, Ogawa K, Watanabe Y, et al. A prospective cohort study on National Health Insurance beneficiaries in Ohsaki, Miyagi Prefecture, Japan: study design, profiles of the subjects and medical cost during the first year. J Epidemiol 1998;8:258–63.
24. Sakata R, McGale P, Grant EJ, Ozasa K, Peto R, Darby SC. Impact of smoking on mortality and life expectancy in Japanese smokers: a prospective cohort study. BMJ 2012;345:e7093.
25. International Agency for Research on Cancer. International classification of diseases for oncology, 3rd ed. Geneva, Switzerland: World Health Organization; 2000.
26. World Health Organization and International Conference for the Ninth Revision of the International Classification of Diseases. Manual of the international statistical classification of diseases, injuries, and causes of death. Geneva, Switzerland: World Health Organization; 1977.
27. World Health Organization. International classification of diseases and health related problems. 10th revision. Geneva, Switzerland: World Health Organization; 1990.
28. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
29. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
30. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Public Health 1998;88:15–9.
31. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
32. Donington JS, Le QT, Wakelee HA. Lung cancer in women: exploring sex differences in susceptibility, biology, and therapeutic response. Clin Lung Cancer 2006;8:22–9.
33. Kreuzer M, Boffetta P, Whitley E, Ahrens W, Gaborieau V, Heinrich J, et al. Gender differences in lung cancer risk by smoking: a multicentre case-control study in Germany and Italy. Br J Cancer 2000;82:227–33.
34. International Early Lung Cancer Action Program Investigators, Henschke CI, Yip R, Miettinen OS. Women's susceptibility to tobacco carcinogens and survival after diagnosis of lung cancer. JAMA 2006;296:180–4.
35. Baron JA, La Vecchia C, Levi F. The antiestrogenic effect of cigarette smoking in women. Am J Obstet Gynecol 1990;162:502–14.
36. Sumi C, Longnecker DS, Roebuck BD, Brinck-Johnsen T. Inhibitory effects of estrogen and castration on the early stage of pancreatic carcinogenesis in Fischer rats treated with azaserine. Cancer Res 1989;49:2332–6.
37. Sumi C, Brinck-Johnsen T, Longnecker DS. Inhibition of a transplantable pancreatic carcinoma by castration and estradiol administration in rats. Cancer Res 1989;49:6687–92.
38. Lee E, Horn-Ross PL, Rull RP, Neuhausen SL, Anton-Culver H, Ursin G, et al. Reproductive factors, exogenous hormones, and pancreatic cancer risk in the CTS. Am J Epidemiol 2013;178:1403–13.
39. Andersson G, Borgquist S, Jirstrom K. Hormonal factors and pancreatic cancer risk in women: the malmo diet and cancer study. Int J Cancer 2018; 143:52–62.
40. Ito H, Matsuo K, Tanaka H, Koestler DC, Ombao H, Fulton J, et al. Nonfilter and filter cigarette consumption and the incidence of lung cancer by histological type in Japan and the United States: analysis of 30-year data from population-based cancer registries. Int J Cancer 2011; 128:1918–28.
41. Heinen MM, Verhage BA, Goldbohm RA, van den Brandt PA. Active and passive smoking and the risk of pancreatic cancer in the Netherlands Cohort Study. Cancer Epidemiol Biomarkers Prev 2010;19:1612–22.
42. Fukumoto K, Ito H, Matsuo K, Tanaka H, Yokoi K, Tajima K, et al. Cigarette smoke inhalation and risk of lung cancer: a case-control study in a large Japanese population. Eur J Cancer Prev 2015;24:195–200.
43. Vrieling A, Bueno-de-Mesquita HB, Boshuizen HC, Michaud DS, Severinsen MT, Overvad K, et al. Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European prospective investigation into cancer and nutrition. Int J Cancer 2010;126: 2394–403.
44. Ben-Zaken Cohen S, Pare PD, Man SF, Sin DD. The growing burden of chronic obstructive pulmonary disease and lung cancer in women: examining sex differences in cigarette smoke metabolism. Am J Respir Crit Care Med 2007;176:113–20.
45. Ando M, Wakai K, Seki N, Tamakoshi A, Suzuki K, Ito Y, et al. Attributable and absolute risk of lung cancer death by smoking status: findings from the Japan Collaborative Cohort Study. Int J Cancer 2003;105:249–54.
46. Wakai K, Inoue M, Mizoue T, Tanaka K, Tsuji I, Nagata C, et al. Tobacco smoking and lung cancer risk: an evaluation based on a systematic review of epidemiological evidence among the Japanese population. Jpn J Clin Oncol 2006;36:309–24.
47. Matsuo K, Ito H, Yatabe Y, Hiraki A, Hirose K, Wakai K, et al. Risk factors differ for non-small-cell lung cancers with and without EGFR mutation: assessment of smoking and sex by a case-control study in Japanese. Cancer Sci 2007;98:96–101.