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Public Health Report

Cigarette Smoking and Pancreas Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence in the Japanese Population

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Objective: Cigarette smoking has been recognized as an important risk factor for pancreas cancer, but the magnitude of the association may vary among geographical areas. Therefore, we reviewed epidemiologic studies on the association between cigarette smoking and pancreas cancer in the Japanese population.

Methods: Original data were obtained from MEDLINE searched using PubMed or from searches of the *Ichushi* database, complemented with manual searches. Evaluation of associations was based on the strength of evidence ('convincing', 'probable', 'possible' or 'insufficient') and the magnitude of association ('strong', 'moderate', 'weak' or 'no association'), together with biological plausibility as previously evaluated by the International Agency of Research on Cancer.

Results: We identified four cohort studies and three case–control studies. All cohort studies consistently showed positive associations between pancreas cancer and cigarette smoking, although statistical significance in each study is variable. Most of the cohort studies consistently showed that cigarette smoking had a dose–response relationship with pancreas cancer. One case–control study showed a strong positive association, but the rest did not show any association. Meta-analysis of seven studies indicated that a summary estimate for ever smoking relative to never smoking was 1.68 (95% confidence interval: 1.38–2.05).

Conclusions: We conclude that there is convincing evidence that cigarette smoking moderately increases the risk of pancreas cancer in the Japanese population.

Key words: systematic review – epidemiology – cigarette smoking – pancreas cancer – Japanese

BACKGROUND

An association between cigarette smoking and the risk of pancreas cancer has been consistently reported from all over the world. In the evaluation by the International Agency for Research on Cancer (IARC), tobacco smoke is classified as a Group 1 carcinogenic agent to humans causing cancer including pancreas cancer (1). Thus, cigarette smoking is one of the internationally well-established risk factors of pancreas cancer.

On the other hand, the risk of pancreas cancer by cigarette smoking might vary among geographical areas because of a large variability in the patterns of tobacco consumption across countries. Genetic differences might also influence association between smoking and pancreas cancer risk. Therefore, the magnitude of the association between cigarette smoking and pancreas cancer in the Japanese population might differ from that in other regions.

We review epidemiological studies on cigarette smoking and pancreas cancer risk among Japanese. This report is one of a series of articles by our research group (2–17), which is investigating the association between lifestyle and the major types of cancer in Japan.

METHODS

Search of Research on the Subject

The details of the evaluation method have been described elsewhere (2). In brief, original data for this review were identified through searches of the MEDLINE (PubMed) and *Ichushi (Japana Centra Revuo Medicina)* databases, complemented by manual searches of references from relevant articles where necessary. All epidemiologic studies on the association between cigarette smoking and pancreas cancer incidence/mortality among the Japanese from 1950 (or 1983 for the *Ichusi* database) to June 2011, including papers in press if available, were identified using the following as keywords: cigarette, smoking, pancreas, pancreas cancer, cohort, follow-up, case–control, Japan and Japanese. Papers written in either English or Japanese were reviewed, and only studies on Japanese populations living in Japan were included. The individual results were summarized in tables separately as cohort or case–control studies. In the case of multiple publications of analyses of the same or overlapping data sets, only data from the largest or the most recent studies were included, and incidence was also given priority in a single publication describing both incidence and mortality.

Evaluation of Strength of Association Between Cigarette Smoking and Pancreas Cancer Risk

An evaluation was made based on the magnitudes of association and the strength of evidence. First, the former was assessed by classifying the relative risk (RR) in each study into the following four categories, while considering statistical significance (SS) or no statistical significance (NS), as strong (symbol ↓↓↓ or ↑↑↑), <0.5 or >2.0 (SS); moderate (symbol ↓↓ or ↑↑), either (i) <0.5 or >2.0 (NS), (ii) >1.5 to 2 (SS) or (iii) 0.5 to <0.67 (SS); weak (symbol ↓ or ↑), either (i) >1.5 to 2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67 to 1.5 (SS); or no association (symbol –), 0.67 to 1.5 (NS). When the multiple RRs were shown in the single study, we considered the largest RR. Criteria for the magnitude of association are summarized in Table 1. After this process, the strength of evidence was evaluated in a similar manner to that used in the WHO/FAO Expert Consultation Report (18), where evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. In brief, the following criteria were used (2). Convincing: evidence based on a substantial number between exposure and disease, with little or no evidence to the contrary, with a biologically plausible association. Probable: evidence based on epidemiologic studies showing fairly consistent associations, but with perceived shortcomings in the available evidence or some evidence to the contrary that precludes a more definite judgment. Possible: evidence based mainly on findings from case–control and cross-sectional studies, requiring more studies to support the tentative associations, which should also be biologically plausible. Insufficient: evidence based on findings of a few studies that are suggestive, but insufficient to establish an association, requiring more well-designed research to support the tentative associations. We assumed that biological plausibility corresponded to the judgment of the recent evaluation from the IARC (1). The final judgment is made based on the consensus of research group members.

Quantitative Evaluation of Association by Meta-analysis

In addition, when there was 'convincing' or 'probable' evidence of a positive or inverse association, a meta-analysis was conducted to obtain summary estimates of the

Table 1. Evaluation of the magnitude of association in the present report

Magnitude of association	Definition	Statistical significance	Symbol
Strong	$RR < 0.5$ or $RR > 2.0$	SS	↑↑↑ or ↓↓↓
Moderate	$RR < 0.5$ or $RR > 2.0$	NS	↑↑ or ↓↓
	$1.5 < RR \leq 2.0$	SS	
	$0.5 \leq RR < 0.67$	SS	
Weak	$1.5 < RR \leq 2.0$	NS	↑ or ↓
	$0.5 \leq RR < 0.67$	NS	
	$0.67 \leq RR \leq 1.5$	SS	
No association	$0.67 \leq RR \leq 1.5$	NS	—

RR, relative risk; SS, statistically significant; NS, not statistically significant.

Table 2. Cigarette smoking and pancreas cancer risk, cohort studies among Japanese population

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI)	*P* value for trend	Confounding variables considered	Comments
		Number of subjects for analysis, sex, age	Source of subjects	Event followed	Number of incident cases or deaths						
Akiba and Hirayama (22)	1965–81 (17 years)	122 261 men	Population-based	Death	312 men	Never smoker	54	1.0	0.04	Age, prefecture, occupation, attained age (5-year interval), observation period (1996–69, 70–73, 74–77, 78–81)	
		142 857 women	Kagosihima			1–4 cigs/day	4	1.1 (0.3–2.7)			
		≥40 years old	Okayama			5–14 cigs/day	112	1.5 (1.1–2.1)			
			Hyogo			15–24 cigs/day	137	1.6 (1.2–2.2)			
			Osaka			25–34 cigs/day	10	1.2 (0.6–2.2)			
			Aichi			35+ cigs/day	5	1.3 (0.4–2.9)			
			Miyagi								
					232 women	Never smoker	198	1.0	0.02		
						1–4 cigs/day	2	0.6 (0.1–1.9)			
						5–14 cigs/day	28	1.9 (1.2–2.8)			
						15+ cigs/day	4	1.4 (0.4–3.4)			
Lin et al. (23)	1988–97 (10 years)	46 465 men	Population-based	Death	120 men	Never	19	1.0	Not described	Age, BMI, DM history and history of gallbladder diseases	
		64 327 women	45 areas in Japan		Ex-smoker	33	1.1 (0.6–1.9)				
		40–79 years	JACC study			Current smoker	68	1.6 (0.95–2.6)			
						Never	19	1.0	0.59		
						1–19 cigs/day	30	1.6 (0.91–2.9)			
						20–39 cigs/day	29	1.3 (0.74–2.4)			
						40+ cigs/day	7	3.3 (1.38–8.1)			
						Never	19	1.0	0.63		
						≥26 started age	8	1.5 (0.65–3.4)			
						23–25	8	1.3 (0.57–2.9)			
						20–22	38	1.7 (0.95–2.9)			
						<20	11	1.7 (0.82–3.7)			
						Never	19	1.0	0.92		
						<25 years smoking	2	1.3 (0.27–6.2)			
						25–34 years	9	2.0 (0.80–4.9)			
						35–44 years	25	1.7 (0.91–3.2)			
						45+	29	1.5 (0.81–2.7)			
						Non-smoker	19	1.0	0.53		
						<20 pack-years	9	2.0 (0.89–4.4)			

						20–39	29	1.7 (0.95–3.1)		
						40–59	20	1.4 (0.73–2.6)		
						>60	7	1.7 (0.70–4.0)		
					105 women	Never	92	1.0	Not described	
						Ex-smoker	4	1.8 (0.67–5.0)		
						Current smoker	9	1.7 (0.85–3.4)		
Luo et al. (24)	Cohort 1	47 499 men	Population-based	Incidence	128 men	Never	19	1.0		
	1990–2003	52 171 women	11 public health			Former	31	1.4 (0.8–2.5)	0.01	Adjusted for age, alcohol drinking (never, occasionally, former, daily <245 g/w, daily ≥245 g/w), history of DM, BMI (14 to <21, 21 to <25, 25+), history of cholelithiasis
		Cohort 1	Centers in Japan			Current	78	1.8 (1.1–3.0)		
	Cohort 2	40–59 years				<30 pack-years	24	1.5 (0.8–2.7)		
	1993–2003	Cohort 2				≥30 pack-years	54	2.0 (1.2–3.4)		
		40–69 years								
					96 women	Never	87	1.0	Not described	
						Past	2	1.7 (0.4–7.1)		
						Current	7	2.0 (0.9–4.4)		
Nakamura et al. (25)	1992–99	14 427 men	Population-based	Death	33 men	Smoking status at baseline		Not described		Adjusted for age, body mass index, history of diabetes mellitus
		17 125 women	Takayama study			Never	4	1.00		
		≥35 years				Former	7	1.43 (0.29–7.07)		
						Current	19	3.81 (0.88–16.6)		
					33 men	Years of smoking			0.18	
						≤30	3	1.03 (0.20–5.38)		
						≥31	16	2.61 (0.87–7.84)		
					33 men	No. of cigarettes per day			0.40	
						≤20	6	5.25 (1.06–26.1)		
						≥21	13	3.53 (0.78–16.1)		
					19 women	Smoking status at baseline		Not described		
						Never	9	1.00		
						Former	2	1.70 (0.21–13.5)		
						Current	5	4.77 (1.58–14.4)		
					19 women	Years of smoking			0.001	
						≤20	2	2.47 (0.52–11.7)		
						≥21	3	9.49 (2.56–35.2)		
					19 women	No. of cigarettes per day			0.005	

Continued

Table 2. *Continued*

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI)	*P* value for trend	Confounding variables considered
		Comments	Number of subjects for analysis, sex, age	Source of subjects	Event followed					
Number of incident cases or deaths										
						≤10	2	3.78 (0.81–17.7)		
						≥11	3	5.91 (1.56–22.4)		

BMI, body mass index; DM, diabetes mellitus.

association. In general, studies that reported RRs and their confidence intervals (CIs) by comparing ever smokers with never or non-smokers were included in the meta-analysis. In case the subject study reported RRs separately according to multiple smoking status or levels, we estimated summary RRs for ever smokers relative to never or non-smokers by meta-analysis within the study, and the study-specific summary RR was included in the final meta-analysis. Studies without information on CIs and different reference categories were excluded from the meta-analysis. A general variance-based method was used to estimate summary statistics and their 95% CIs. Heterogeneity among studies was examined by testing the *Q*-statistic (19), with the model used to determine the summary RR and its 95% CI, namely a random- or fixed-effect model, selected according to the SS of the *Q*-statistic. A publication bias was assessed by using a funnel plot and an Egger's test (20). Meta-analysis was done using the 'metan' and 'metabias' command of STATA statistical package version 11 (StataCorp LP, College Station, TX, USA).

MAIN FEATURES AND COMMENTS

After excluding one cohort study (21) due to the analysis of the overlapping data sets, we identified four cohort studies (22–25) (Table 2) and three case–control studies (26–28) (Table 3). All the cohort studies (26–28) and one case–control study (28) presented the results by sex. The remaining two case–control studies presented the results for men and women combined (26,27).

A summary of the magnitude of association for the cohort and case–control studies is shown in Tables 4 and 5, respectively. All the cohort studies consistently showed positive association between cigarette smoking and pancreas cancer, although the significance of association varied across studies. Moreover, most of the cohort studies showed the dose–response or duration–response relationships between cigarette smoking and pancreas cancer risk in men (22,24) and in women (25). Among three case–control studies, one study showed strong association between cigarette smoking and pancreas cancer risk (26). This study demonstrated a strong association between passive smoking in youth and pancreas cancer risk. Another case–control study showed a dose–response relationship in combined analysis of males and females or analysis of males only (28), although each point estimate for smoking did not reach SS.

In a comprehensive review by World Cancer Research Fund and American Cancer Research Institute, several risk/protective factors were indicated with the levels of strength of evidence: body fatness as a convincing risk factor, folate-containing foods as a probable protective factor, and abdominal fat and adult attained height as probable risk factors (29). Status of consideration of these factors in the studies we reviewed need to be mentioned. Three out of four cohort studies that we reviewed considered anthropometric

Table 3. Cigarette smoking and pancreas cancer risk, case–control studies among Japanese population

References	Study period	Study subjects				Category	Relative risk (95% CI)	*P* value for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
Mizuno et al. (26)	1989–90	Hospital-based Natl Cancer Ctr, Chiba Univ, Shinshu Univ, Cancer Inst Kobe Univ, Satitama Cancer Ctr, Nagasaki Univ	Cases: those diagnosed as pancreatic cancer pathologically radiographically or serologically. Controls: age, sex and institution matched controls with benign disease	124 (68 males, 56 females) (age range 40–79)	124 (68 males, 56 females) (age range 40–79)	Non-smoker	1.00	Not described	Matched for age, sex and institution. Adjusted for age and sex	
						Ex-smoker	1.22 (0.44–3.39)			
						Light smoker <13 cigs/day	4.50 (1.53–13.18)			
						Medium smoker 13–22 cigs/day	2.57 (1.0–6.51)			
						Heavy smoker 23+ cigs/day	2.56 (0.93–7.04)			
						(Passive smoking in youth +)				
						Non-smoker	1.00	Not described	Age and sex	
						Ex-smoker	1.65 (0.35–7.78)			
						Light smoker <13 cigs/day	8.86 (1.95–40.18)			
						Medium smoker 13–22 cigs/day	4.15 (1.05–16.46)			
						Heavy smoker 23+ cigs/day	3.97 (0.95–16.69)			
						(Passive smoking in youth −)				
						Non-smoker	1.00	Not described	Age and sex	
						Ex-smoker	0.94 (0.19–4.55)			
						Light smoker <13 cigs/day	1.81 (0.26–12.73)			
						Medium smoker 13–22 cigs/day	1.35 (0.30–6.14)			
						Heavy smoker 23+ cigs/day	2.28 (0.28–18.32)			
Ohba et al. (27)	1987–92	Hospital-based (Sapporo Medical University)	Cases: those diagnosed as pancreatic cancer pathologically or clinically) Controls: those randomly selected by phone matched for sex, age residence)	123 (no info for sex. Mean age 64.4 years)	246 (no info. available for sex, and age)	Smoking status		Not described	Matched for age	Description only in text

Continued

Table 3. *Continued*

References	Study period	Study subjects				Category	Relative risk (95% CI)	*P* value for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
						Never	1.0		Sex and residence. No adjustment	
						Ex-smoker	1.25 (0.73–2.13)			
						Current smoker	1.28 (0.81–2.03)			
Inoue et al. (28)	1988–99	Hospital-based (Aichi Cancer Center Hospital)	Cases: first visit out-patients diagnosed as having pancreatic cancer. Controls: first visit out-patients confirmed to not to have cancer	200 (122 males, 78 females) (age: male mean 60.2, range 30–84, female 61.1, 32–85)	2000 (males 1220, females 780) (age: male mean 60.1, 32–82, female 60.8, 30–89)	Both sex		Not described	Age–sex matched. Adjusted for age, sex, family history of pancreatic cancer, past/present history of DM, regular exercise, bowel habits, raw vegetable intake and alcohol drinking	
						Never	1.0			
						Ever	0.92 (0.62–1.37)			
						Never	1.0	Not described		
						Former	0.60 (0.35–1.00)			
						Current	1.14 (0.75–1.74)			
						Never	1.0	<0.05		
						<20 cigs/day	0.99 (0.62–1.57)			
						20+ cigs/day	1.65 (0.95–2.8)			
						Never	1.0	Not described		
						20+ years started age	1.10 (0.71–1.70)			
						18–19 years	1.33 (0.63–2.79)			
						<18 years	1.61 (0.50–5.18)			
						Never	1.0	Not described		
						<20 years (duration)	0.90 (0.25–3.22)			
						20–39 years	1.34 (0.82–2.19)			
						40+ years	0.99 (0.57–1.72)			
						Never	1.0	Not described		
						<20 pack-years	0.74 (0.33–1.64)			
						20–39 pack-years	1.22 (0.71–2.10)			
						40+ pack-years	1.30 (0.77–2.17)			
						Male		Not described		
						Never	1.0			
						Ever	0.80 (0.50–1.28)			
						Never	1.0	Not described		
						Former	0.56 (0.32–1.00)			
						Current	0.99 (0.60–1.63)			

Never	1.0	<0.05
<20 cigs/day	0.77 (0.44–1.35)	
20+ cigs/day	1.51 (0.83–2.72)	
Never	1.0	Not described
20+ years started age	0.91 (0.54–1.52)	
18–19 years	1.34 (0.62–2.92)	
<18 years	1.54 (0.47–5.08)	
Never	1.0	Not described
<20 years (duration)	1.00 (0.19–5.36)	
20–39 years	1.19 (0.67–2.12)	
40+ years	0.82 (0.44–1.54)	
Never	1.0	Not described
<20 pack-years	1.00 (0.54–1.86)	
20–39 pack-years	1.15 (0.66–2.02)	
40+ pack-years	0.57 (0.32–1.02)	
Female		Not described
Never	1.0	
Ever	1.26 (0.62–2.56)	
Never	1.0	not described
Former	0.29 (0.04–2.37)	
Current	1.77 (0.83–3.78)	
Never	1.0	Not described
<20 years (duration)	0.67 (0.82–5.45)	
20–39 years	2.10 (0.79–5.61)	
40+ years	2.47 (0.67–9.10)	
Never	1.0	Not described
<20 pack-years	1.43 (0.47–4.37)	
20–39 pack-years	2.40 (0.79–7.26)	
40+ pack-years	1.56 (0.27–9.07)	

Table 4. Summary of the association between cigarette smoking and pancreas cancer risk, cohort study

References	Study period	Study population						
		Sex	Number of subjects	Age range (years)	Event	Number of incident cases or deaths	Category	Magnitude of association
Akiba and Hirayama (22)	1965–81	Men	122 261	40 years or older	Death	312	Cigarettes/day	↑
		Women	142 857	40 years or older	Death	232	Cigarettes/day	↑
Lin et al. (23)	1988–97	Men	46 465	40–79 years	Death	120	Smoking status	↑↑
		Women	64 327	40–79 years	Death	105	Cigarettes/day	↑↑
							Years of smoking	
Luo et al. (24)	Cohort 1	Men	47 499	Cohort 1	Incidence	128	Smoking status	↑↑
	1990–2003	Women	52 171	40–59 years	Incidence	96		↑
	Cohort 2			Cohort 2				
	1993–2003			40–69 years				
Nakamura et al. (25)	1992–99	Men	14 427	35–	Death	33	Smoking status	↑↑
							Years of smoking	↑↑
							No. of cigarettes	↑↑↑
		Women	17 125	35–	Death	19	Smoking status	↑↑↑
							Years of smoking	↑↑↑
							No. of cigarettes	↑↑↑

↑, weak positive association; ↑↑, moderate positive association, ↑↑↑, strong positive association.

Table 5. Summary of the association between cigarette smoking and pancreas cancer risk, case–control study

References	Study period	Study subjects					
		Sex	Age range (years)	Number of cases	Number of controls	Category	Magnitude of association
Mizuno et al. (26)	1989–90	Men and women	40–79	124 (M: 68, F: 56)	124 (M: 68, F: 56)	Smoking status	↑↑↑
Ohba et al. (27)	1987–92	Men and women	Not specified	123 (sex not specified)	246 (sex not specified)	Smoking status	–
Inoue et al. (28)	1988–99	Men	30–84	200 (M: 122, F: 78)	2000 (M: 1220, F: 780)	Smoking status	–
		Women	32–85			Smoking status	–

↑↑↑, strong positive association; –, no association.

factors in their evaluation and they consistently showing significant association about smoking even after adjustment of. No studies considered folate consumption, and it is difficult to quantitatively judge the effect of this lack of consideration in our evaluation. This point should be addressed in a future pooled analysis which can consider folate consumption.

In addition to the narrative review, we conducted a meta-analysis to clarify the magnitude of alcohol drinking among Japanese (Fig. 1). A random-effect model was selected for the meta-analysis because heterogeneity tested by the Q-statistic was significant ($Q = 1.322$, $P = 0.04$). Egger's test to evaluate publication bias was not significant ($P = 0.229$). Ever smokers had a significantly higher risk than never smokers (RR 1.68, 95% CI: 1.38–2.05). This result was consistently observed when we limit studies to only cohort studies (RR 1.79, 13.9–2.30). Smoking often confounds with sex and smoking was adjusted in all the studies. Sex-stratified analysis with data available (22–25,28) showed consistent association in men (1.57, 1.30–1.89) and women (1.83, 1.35–2.48). The review by IARC did not report a quantitative summary of association; however, summary statistics in this study are within the range of reported RRs in the reviewed studies (1). This might suggest that an impact of smoking on pancreas cancer risk in the Japanese population is similar to that in other populations.

There were several potential limitations in the Japanese studies in this systematic review. One methodological issue

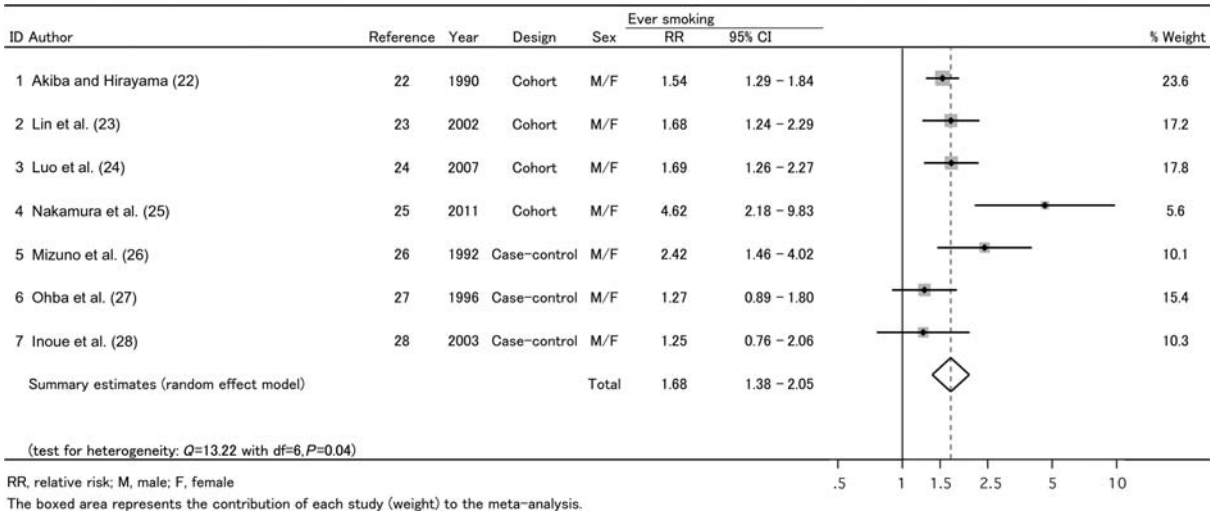

Figure 1. Summary estimates of the association between cigarette smoking and pancreas cancer risk. RR, relative risk; CI, confidence interval; M, male; F, female. The boxed area represents the contribution of each study (weight) to the meta-analysis.

was assessment of smoking exposures, which was investigated by a questionnaire in all cohort and case–control studies; therefore, it is difficult to completely exclude possible misclassification. Moreover, the definition and categorization of smoking exposure were heterogeneous across studies. These might bias the measure of association between cigarette smoking and pancreas cancer risk toward the null hypothesis. Recall bias might intensify the association; however, it would be unlikely because the significant association we observed was mainly from cohort studies.

Lastly, the meta-analysis showed that ever smokers had significantly increased risk for pancreas cancer than never smokers. As the quantitative measurement of cigarette consumption was heterogeneous across studies, we could not evaluate the dose–response or frequency–response relationships within the meta-analysis. Therefore, a pooled analysis using common cigarette-smoking categories is essential to quantify a dose–response or frequency–response relationship in the Japanese population.

EVALUATION OF EVIDENCE ON CIGARETTE SMOKING AND PANCREAS CANCER RISK IN JAPANESE

From these results, we conclude that there is convincing evidence that cigarette smoking moderately increases the risk of pancreas cancer in the Japanese population.

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Conflict of interest statement

None declared.

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Appendix

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