					107 men	Lowest	32	1.00		
						Second	27	0.92 (0.54–1.54)		
						Third	20	0.75 (0.42–1.33)		
						Highest	28	0.89 (0.53–1.51)	0.69	
					59 women	Lowest	17	1.00		
						Second	15	1.09 (0.52–2.29)		
						Third	11	0.77 (0.34–1.74)		
						Highest	16	1.37 (0.66–2.85)	0.40	
					Rectum					
					92 men	Lowest	20	1.00		
						Second	26	1.36 (0.74–2.49)		
						Third	26	1.64 (0.90–2.99)		
						Highest	21	1.06 (0.56–2.00)	0.97	
					56 women	Lowest	12	1.00		
						Second	16	1.72 (0.76–3.89)		
						Third	10	1.20 (0.49–2.95)		
						Highest	18	2.23 (0.99–5.01)	0.06	
Takahashi et al. (15)	1990–97	41 988 (20 519 men, 21 469 women)	Miyagi study (Miyagi prefecture)	Incidence	Colorectum	Hours per day[b]				Age, smoking, alcohol intake, body mass index, family history of colorectal cancer, education, sports or exercise, meat intake, intakes of green or yellow vegetables and oranges
					166 men	<0.5	55	1.00		
						0.5–1	51	1.06 (0.72–1.57)		
						>1	60	0.57 (0.38–0.83)	0.003	
					94 women	<0.5	23	1.00		
						0.5–1	29	1.32 (0.76–2.30)		
						>1	42	1.02 (0.60–1.75)	0.91	
					Colon					
					101 men	<0.5	40	1.00		
						0.5–1	30	0.81 (0.50–1.32)		
						>1	31	0.38 (0.23–0.64)	<0.001	
					50 women	<0.5	10	1.00		
						0.5–1	15	1.78 (0.77–4.10)		
						>1	25	1.33 (0.60–2.94)	0.63	
					Rectum					

Continued

Table 1. *Continued*

Reference	Study period	Study population				Category	No. among cases or deaths	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered
		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths					
					65 men	<0.5	15	1.00		
						0.5–1	21	1.75 (0.88–3.50)		
						>1	29	1.07 (0.55–2.06)	0.94	
					44 women	<0.5	13	1.00		
						0.5–1	14	1.18 (0.54–2.58)		
						>1	17	0.82 (0.39–1.71)	0.55	

[a]Estimated from four levels of physical activity: heavy physical work or strenuous exercise, walking and standing, sedentary and sleep or others.
[b]Estimated from time spent on walking.

association of physical activity against colon cancer, one (19) showed a weak protective association with proximal colon cancer and another (21) exhibited a moderate to strong protective association with distal colon cancer. A protective association was also observed for rectal cancer, although the association was generally less evident than for colon cancer (16–18,21). The remaining study examining the combined colon and rectal cancer only showed no association (20).

We should discuss several methodological issues regarding the evidence of the relationship between physical activity and colorectal cancer in general and in particular for Japanese studies. First, we did not conduct a meta-analysis to calculate summary effect size of the association between physical activity and risk of colorectal cancer. This is because we found a large discrepancy among the studies reviewed here regarding methods used in the ascertainment of physical activity and categories created to group study participants. Secondly, attention should be focused when interpreting the findings of case–control studies. Case–control studies are prone to recall bias, leading to a difference in reported levels of physical activity between cases and controls. Specifically, a protective association between physical activity and colorectal cancer is overestimated if patients with colorectal cancer tend to underreport physical activity in the past, due to the influence of their disease status on recall, compared with healthy control individuals. Thirdly, most of the case–control studies reviewed in the present paper selected controls from among patients or participants of health checkups or screening, which might have resulted in various extents of selection bias among studies. Fourthly, few case–control studies have controlled for factors including intakes of dietary fiber, folate and vegetables, which have been favorably associated with colorectal cancer risk (22,23). Failure to account for these factors may result in a spurious association between physical activity and the risk of colorectal cancer. However, both cohort studies in the present review showed a strong, inverse association between physical activity and colon cancer in men even after adjustment of potentially important risk or protective factors of colorectal cancer. Fifthly, cohort studies possess their constitutional drawbacks. For one, physical activity level assessed in a prospective cohort design would be non-differentially misclassified, leading to a dilution of association. Furthermore, only baseline measurement of physical activity was used as an exposure variable in the two Japanese cohort studies, but physical activity level may change over the life course. Finally, as with any review based on published articles, we cannot rule out a possibility of publication bias, which would work to produce spurious association even in the case of no association. However, the effect of such bias may not largely distort our conclusion because most case–control studies in this review reported results not only for physical activity but also for other lifestyle factors within the same paper or in other independent ones.

A protective association between physical activity and colorectal cancer is supported by a number of biologic mechanisms. Main hypothesized mechanisms include

Table 2. Physical activity and colorectal cancer risk, case–control study among Japanese populations

Reference	Study period	Study subjects				Category	Odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	No. of cases	No. of controls					
Kato et al. (16)	1979–87	Registry based (Aichi Cancer Registry)	Cases: histologically confirmed (90%); controls: patients with other sites of cancer excluding known alcohol-related cancers (mouth, pharynx, esophagus, liver and unknown sites)	Colon		Occupational activity			Adjusted for age	Each occupation was classified according to the proportion of physically active time on the job
				1716 men	16 600 men	High	1.00			
						Moderate	1.79 (1.50–2.15)			
						Low	1.87 (1.58–2.23)	NA		
				Proximal colon						
				445 men	16 600 men	High	1.00			
						Moderate	1.76 (1.24–2.48)			
						Low	1.92 (1.38–2.67)	NA		
				Distal colon						
				756 men	16 600 men	High	1.00			
						Moderate	1.70 (1.33–2.19)			
						Low	1.52 (1.19–1.94)	NA		
				Rectum						
				1611 men	16 600 men	High	1.00			
						Moderate	1.30 (1.10–1.55)			
						Low	1.38 (1.17–1.62)	NA		
Kato et al. (17)	1986–90	Hospital based (Aichi Cancer Center Hospital)	Cases: histologically confirmed cases among examinees of colonoscopy at the hospital; controls: population controls selected through the telephone directories	Colon		Sports activity			Adjusted for residence, sex and age (5-year age group)	*Common controls for cases of cancer of the colon and rectum
				132 (M: 79, F: 53)	578 (M: 377, F: 201)*	Almost no activity	1.00			
						<1/week	0.72 (0.44–1.19)			
						≥1/week	0.55 (0.33–0.89)			
						Occupational activity				
						Sedentary	1.00			
						Moderate	0.58 (0.37–0.90)			
						High	0.51 (0.30–0.87)			
				Rectum		Sports activity				

Continued

Table 2. *Continued*

Reference	Study period	Study subjects				Category	Odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	No. of cases	No. of controls					
				91 (M: 60, F: 31)	578 (M: 377, F: 201)*	Almost no activity	1.00			
						<1/week	0.86 (0.50–1.50)			
						≥1/week	0.54 (0.30–0.97)			
						Occupational activity				
						Sedentary	1.00			
						Moderate	1.24 (0.72–2.15)			
						High	0.70 (0.36–1.38)			
Kotake et al. (18)	1992–94	Hospital based (10 hospitals in Kanto region)	Cases: histologically confirmed cases; controls: screening controls and hospital controls, including cancer patients	Colon		Occupational physical activity			Matched for sex, age (5-year age group)	Risk estimates for intermediate categories are not shown.
				187 (M: 111, F: 76)	187 (M: 111, F: 76)	Very active	1.0			
						Sedentary	1.1 (0.30–2.84)			
						Physical exercise				
						Often	1.0			
						Seldom	0.9 (0.17–1.89)			
				Rectum		Occupational physical activity				
				176 (M: 103, F: 73)	176 (M: 103, F: 73)	Very active	1.0			
						Sedentary	1.9 (0.66–5.54)			
						Physical exercise				
						Often	1.0			
						Seldom	1.0 (0.25–8.01)			
Inoue et al. (19)	1988–92	Hospital based (Aichi Cancer Center Hospital)	Cases: histologically confirmed cases; controls: first-visit outpatients free from cancer	Proximal colon		Physical exercise			Adjusted for age	*Common controls for cases of cancer of the colon and rectum
				51 men	8621 men*	≤4/month	1.0			
						>4/month	0.7 (0.4–1.5)			
				43 women	23 161 women*	≤4/month	1.0			
						>4/month	0.5 (0.2–1.5)			
				Distal colon						
				75 men	8621 men*	≤4/month	1.0			
						>4/month	0.7 (0.4–1.3)			
				62 women	23 161 women*	≤4/month	1.0			
						>4/month	1.0 (0.5–2.0)			
				Rectum						
				131 men	8621 men*	≤4/month	1.0			
						>4/month	0.8 (0.5–1.3)			
				70 women	23 161 women*	≤4/month	1.0			
						>4/month	0.7 (0.3–1.4)			

Ping et al. (20)	1986–94	Health checkup based (Tokai University Hospital: health checkup examinees)	Cases: histologically confirmed cases; controls: cancer-free examinees	Colorectum		Exercise			Matched (1:3) for sex, age (±2 years), data of health checking(±3 months) and residence; 35 controls were excluded due to a lack of lifestyle data	The definition of 'lack of exercise' is not stated.
				100 (M: 77, F: 23)	265 (NA)	Not lacking	1.00			
						Lacking	1.39 (0.87–2.20)			
Isomura et al. (21)	2000–03	Hospital based (two university hospitals and six affiliated hospitals	Cases: patients undergoing surgery for a first diagnosis of colorectal cancer; controls: population controls selected using two-stage random sampling method	Colon		Job-related physical activity			The number of control candidates by sex and 10-year age class were determined a priori in accordance with sex and age-specific numbers of incident cases of colorectal cancer in the Osaka Cancer Registry; Adjusted for age, smoking, alcohol use, residence, BMI and non-job physical activities or job-related physical activities	
				248 men	470 men	Sedentary	1.0			
						Moderate	0.9 (0.6–1.4)			
						Hard	0.7 (0.4–1.0)	0.06		
						Non-job physical activity				
						0	1.0			
						0.1–15.9	0.9 (0.6–1.4)			
						16.0+	0.8 (0.5–1.2)	0.22		
				190 women	297 women	Job-related physical activity				
						Sedentary	1.0			
						Active	0.7 (0.4–1.2)	0.18		
						Non-job physical activity				
						0	1.0			
						0.1–15.9	0.9 (0.5–1.5)			
						16.0+	0.8 (0.5–1.4)	0.45		
				Proximal colon		Job-related physical activity				
				88 men	470 men	Sedentary	1.0			
						Moderate	1.2 (0.6–2.2)			
						Hard	0.7 (0.4–1.4)	0.45		
						Non-job physical activity				
						0	1.0			
						0.1–15.9	1.2 (0.6–2.1)			
						16.0+	0.9 (0.5–1.7)	0.69		

Continued

Table 2. *Continued*

Reference	Study period	Study subjects				Category	Odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	No. of cases	No. of controls					
				87 women	297 women	Job-related physical activity				
						Sedentary	1.0			
						Active	1.2 (0.6–2.3)	0.65		
						Non-job physical activity				
						0	1.0			
						0.1–15.9	1.5 (0.7–3.3)			
						16.0+	1.6 (0.7–3.6)	0.41		
				Distal colon		Job-related physical activity				
				159 men	470 men	Sedentary	1.0			
						Moderate	0.8 (0.4–1.4)			
						Hard	0.6 (0.4–1.0)	0.047		
						Non-job physical activity				
						0	1.0			
						0.1–15.9	0.8 (0.5–1.3)			
						16.0+	0.7 (0.4–1.1)	0.19		
				103 women	297 women	Job-related physical activity				
						Sedentary	1.0			
						Active	0.4 (0.2–0.8)	0.02		
						Non-job physical activity				
						0	1.0			
						0.1–15.9	0.7 (0.4–1.3)			
						16.0+	0.6 (0.3–1.1)	0.12		
				Rectum		Job-related physical activity				
				208 men	470 men	Sedentary	1.0			
						Moderate	0.9 (0.5–1.4)			
						Hard	0.6 (0.4–0.9)	0.02		
						Non-job physical activity				
						0	1.0			
						0.1–15.9	0.6 (0.4–0.9)			
						16.0+	0.5 (0.3–0.8)	0.01		

132 women	297 women	Job-related physical activity			
		Sedentary	1.0		
		Active	1.1 (0.6–1.9)	0.81	
		Non-job physical activity			
		0	1.0		
		0.1–15.9	1.2 (0.7–2.3)		
		16.0+	0.9 (0.5–1.8)	0.47	

NA, not available; NS, not significant; M, men; F, women.

prevention of obesity, a strong predictor of colorectal cancer, decreased inflammation, reduced levels of insulin and insulin-like growth factor 1 and modulated immune response (7,24,25). In addition, physical activity has been associated with an increased level of circulating vitamin D (26), which has an anti-carcinogenic effect on colonic epithelial cells (27) and has been related to lower risk of colon cancer (28). Other possible mechanisms include decreased bowel transit time (29), thereby resulting in less exposure of the colon to colonic contents, bile acids and other potential carcinogens. Physical activity was also related to increased prostaglandin $F_2\alpha$ (30) and reduced prostaglandin E_2 (31); the former prevents tumor development in the colon and increases gut motility (32,33), whereas the latter reduces colonic motility and promotes the proliferation of colonic cells (32,34). Moreover, physical activity has been shown to be associated with decreased prevalence of colon adenoma (35), a precursor of colorectal cancer.

The association between physical activity and colorectal cancer in Japanese studies reviewed here is generally in agreement with that of previous reviews (6–10). A consistent dose–response relationship of physical activity to a decreased risk of colon cancer was observed in both cohort and case–control studies. Moreover, agreement exists between Japanese cohort studies (14,15) and previous reviews (6–9) on the lack of association between physical activity and risk of rectal cancer. Results of the present review support a protective role of physical activity in the prevention of colon cancer.

Unlike the protective association of physical activity with colon cancer risk consistently observed here and in previous reviews (6–10), the association with rectal cancer was mixed in our review. Consistent with previous reports (6–9), cohort studies reviewed here did not show any association between physical activity and rectal cancer, while the majority of case–control studies reported weak to moderate protective association (16–18,21) and some of the case–control studies exhibited a dose–response relationship (16,17,21). The possible disagreement regarding the association of physical activity with rectal cancer observed in cohort and case–control studies in the present review may be attributed to the difference of study design, as discussed in the methodological section above.

A point of note in the present review is that men showed a stronger protective association of physical activity with colon cancer than women in cohort studies. This observation is in line with numerous studies in other countries on this topic (6–10). We had no clear reason for such sex difference in association. One possible explanation is that men and women differ in terms of the amount, intensity and duration of physical activity engaged. It is conceivable that men tend to be engaged in more strenuous physical activity when compared with women. In addition, women are more likely to participate in housework and childcare, which are difficult to assess precisely. As a result, men may provide more accurate information about their physical activity than women. Epidemiologic evidence suggests that 30–60 min per day of moderate to vigorous intensity physical activity are necessary to reduce colon cancer risk (36).

Table 3. Summary of the association between physical activity and colorectal cancer risk, cohort study

References	Study period	Study population					Magnitude of association[a]		
		Sex	Number of subjects	Ranged age (years)	Event	Number of incident cases or deaths	Colon	Rectum	Colorectum
Lee et al. (14)	1995–02	Men	29 842	40–69	Incidence	290	↓↓↓[b,c,d]	–	↓
		Women	35 180	40–69	Incidence	196	↓[b]	↑↑	–
Takahashi et al. (15)	1990–97	Men	25 279	40–64	Incidence	166	↓↓↓[d]	–	↓↓
		Women	26 642	40–64	Incidence	94	–	–	–

[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; –, no association (see text for more detailed definition); if the magnitude of association differs between occupational and non-occupational activities or between proximal and distal colon, strongest association is reported.
[b]Proximal colon.
[c]Occupational physical activity.
[d]Non-occupational physical activity.

Table 4. Summary of the association between physical activity and colorectal cancer risk, case–control study

Reference	Study period	Study subjects						Magnitude of association[a]		
		Sex	Age range	No. of cases			No. of controls	Colon	Rectum	Colorectum
				Colon	Rectum	Colorectum				
Kato et al. (16)	1979–87	Men	≥20 year	1716	1611	NP	16 600	↓↓[d]	↓[d]	NA
Kato et al. (17)	1986–90	Men and women	Not specified	132	91	NP	578	↓↓[d,e]	↓↓[d]	NA
Kotake et al. (18)	1992–94	Men and women	Not specified	187	176	NP	363	–	↓[d]	NA
Inoue et al. (19)	1988–92	Men	24–86 year	126	131	NP	8621	–[e]	–[e]	NA
		Women	24–88 year	105	70	NP	23 161	↓[b,e]	–[e]	NA
Ping et al. (20)	1986–94	Men and women	40–84 year	NP	NP	100	265	NA	NA	–
Isomura et al. (21)	2000–03	Men	20–74 year	248	208	NP	470	↓↓[c,d]	↓↓[d,e]	NA
		Women	20–74 year	190	132	NP	297	↓↓↓[c,d]	–	NA

NP, not provided; NA, not available; M, men; F, women.
[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; –, no association (see text for more detailed definition); if the magnitude of association differs between occupational and non-occupational activities or between proximal and distal colon, strongest association is reported.
[b]Proximal colon.
[c]Distal colon.
[d]Occupational physical activity.
[e]Non-occupational physical activity.

In conclusion, epidemiological evidence for a protective association of physical activity with colorectal cancer among the Japanese population is more consistent and stronger for colon cancer than for rectal cancer. A protective association with rectal cancer was observed in some case–control studies, but not in cohort studies.

Evaluation of Evidence on Physical Activity and Colorectal Cancer in Japanese

From the results of the present review and based on the hypothesized biological plausibility, we conclude that physical activity probably reduces the risk of colorectal cancer among the Japanese population. More specifically, the evidence for the colon is probable, whereas that for the rectum is insufficient.

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Conflict of interest statement

None declared.

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Appendix

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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 ≤ 2.0	SS	
	0.5 ≤ RR < 0.67	SS	
Weak	1.5 < RR ≤ 2.0	NS	↑ or ↓
	0.5 ≤ RR < 0.67	NS	
	0.67 ≤ RR ≤ 1.5	SS	
No association	0.67 ≤ RR ≤ 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

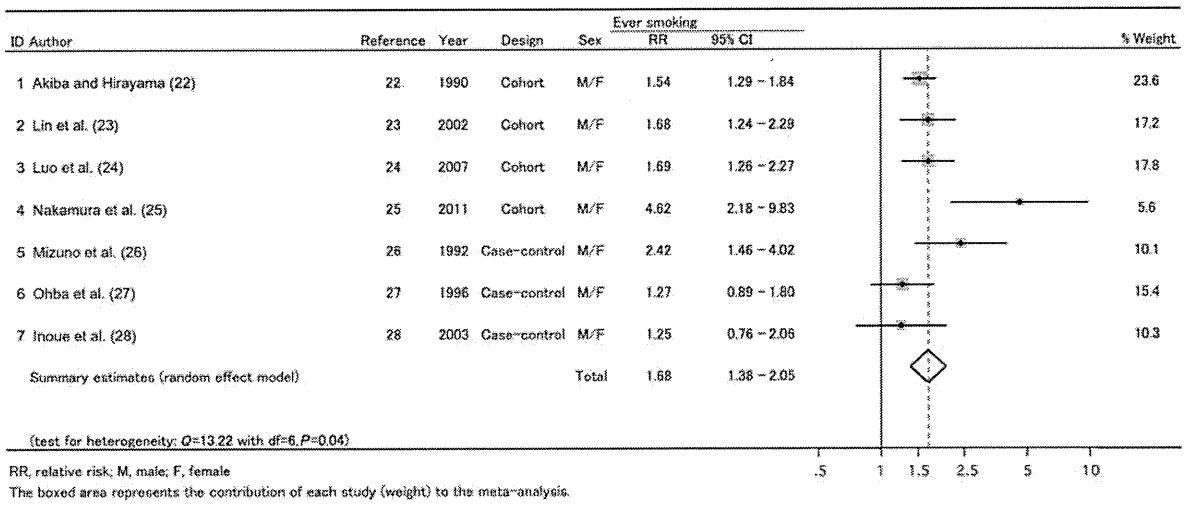

Figure 1. Summary estimates of the association between cigarette smoking and pancreas cancer risk. RR, relative risk; CI, confidence interval; M, male; F, female. The boxed area represents the contribution of each study (weight) to the meta-analysis.

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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