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Public Health Report

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

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Objective: Although cigarette smoking is considered as an important risk factor for esophageal cancer, the magnitude of the association might be varied among geographic areas. Therefore, we reviewed epidemiologic studies on the association between cigarette smoking and esophageal cancer among the Japanese population.

Methods: Original articles were obtained from MEDLINE searched using PubMed or from searches of the *Ichushi* database, complemented by 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 for Research on Cancer.

Results: We identified four cohort studies and 11 case–control studies. All cohort studies and eight case–control studies showed strong positive associations between esophageal cancer and cigarette smoking. All cohort studies and five case–control studies showed that cigarette smoking had dose–response relationships with esophageal cancer. Meta-analysis of 12 studies indicated that the summary estimate for ever smokers relative to never smokers was 3.01 (95% confidence interval: 2.30–3.94). Summary relative risk for current and former smokers relative to never smokers was 3.73 (2.16–6.43) and 2.21 (1.60–3.06), respectively.

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

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

BACKGROUND

Consistent positive associations between cigarette smoking and esophageal cancer were reported from all over the world. In previous comprehensive risk evaluation by the Office of Surgeon General, the risk among current smokers was up to seven or eight times higher than the risk for lifetime non-smokers (1). In the most recent evaluation by the International Agency for Research on Cancer (IARC), cigarette smoking was evaluated as Group 1: carcinogenic to humans (2,3). Thus, cigarette smoking is a well-established risk factor for esophageal cancer.

On the other hand, the risk of esophageal cancer might vary among geographic areas. In addition, the distribution of histologic subtypes differs across countries. Squamous cell carcinoma is still prevalent in Japanese population, whereas adenocarcinoma is getting prevalent in Western population (4–7). The variability in cigarette consumption or in composition of ethnicities might be the causes of the difference. Therefore, the magnitude of association between cigarette smoking and esophageal cancer among Japanese population might differ from the other regions.

We reviewed epidemiologic studies on cigarette smoking and esophageal cancer risk among Japanese. This report is one of a series of articles by our research group (8–14), which is investigating the association between lifestyle and the major types of cancer in Japan.

PATIENTS AND METHODS

Searching of Subject Researches

The details of the evaluation method have been described elsewhere (8). In brief, original articles 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 esophageal cancer incidence/mortality among the Japanese from 1950 (or 1983 for the *Ichushi* database) to June 2011, including papers in press if available, were identified using the following as keywords: cigarette, smoking, esophagus, esophageal 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 the 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.

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

The 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) >1.5–2 (SS) or (iii) 0.5 to <0.67 (SS); weak (symbol ↓ or ↑), either (i) >1.5–2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association (symbol –), 0.67–1.5 (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 manner similar to that used in the WHO/FAO Expert Consultation Report (15), where evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. In brief, the following criteria were used (8): 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 (2,3). 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, meta-analysis was

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.

conducted to obtain summary estimates of the association. In general, studies that reported RRs and their confidence intervals (CIs) by comparing ever smokers with never 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 RR for ever smokers relative to never 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 meta-analysis. General variance-based methods were used to estimate summary statistics and their 95% CIs. Heterogeneity among studies was examined by testing the Q-statistic (16), with the model used to determine summary RR and its 95% CI, namely a random- or fixed-effect model, selected according to the significance in the Q-statistic. Publication bias was assessed by using the funnel plot and Egger's test (17). Meta-analysis was done using the 'metan' and 'metabias' command of STATA statistical package version 10 (Stata Corp. LP, College Station, TX, USA).

MAIN FEATURES AND COMMENTS

After excluding 2 cohort studies (18,19) and 1 case–control study (20) due to the analysis of the overlapping datasets, we identified 4 cohort studies (21–24) (Table 2) and 11 case–control studies (25–35) (Table 3). Of these cohort studies, one (21) presented the results by sex and three (22–24) presented the results for men only. Among case–control studies, one (26) presented the results by sex, five (25,29,30,34,35) for men and women combined, three (27,28,31) for men only and two (32,33) for women only.

A summary of the magnitude of association for the cohort studies and case–control studies was shown in Tables 4 and 5, respectively. All cohort studies (21–24) and 8 of 11 case–control studies (25,26,28,29,31,33–35) showed strong positive association between cigarette smoking and esophageal cancer. Moreover, the dose–response relationships between cigarette smoking and esophageal cancer risk were shown in all cohort studies (21–24) and five case–control studies (25,28,29,33,35). Only one cohort study (21) and one case–control study (28) showed the reversal of risk after smoking cessation. The RRs for years of quitting smoking were inconsistent between two studies.

We conducted a meta-analysis to clarify the magnitude of cigarette smoking among Japanese (Figs 1 and 2). Two studies were excluded because of the different reference category (31,34). The random-effect model was selected for the meta-analysis because heterogeneity tested for Q-statistics was significant ($Q = 42.59$, $P < 0.001$). Although Egger's test for publication bias was not significant ($P = 0.148$), funnel plot showed asymmetry (Fig. 3). Ever smokers had significantly higher summary RR than never smokers (RR 3.01, 95% CI 2.30–3.94) (Fig. 1). Seven studies (22–24,27–30) showed the RR of current and former smokers compared with never smokers. Summary RR for current and former smokers were 3.73 (95% CI, 2.16–6.43) and 2.21 (1.60–3.06), respectively (Fig. 2). When we limit the analysis to cohort studies, summary RRs for ever smokers and current smokers were 2.97 (95% CI, 2.12–4.16) and 4.20 (2.83–6.23), respectively. Several studies did not adjusted alcohol consumption in their analyses; therefore, we conducted the meta-analysis only among the studies adjusted for alcohol consumption. After excluding seven studies (21,22,25,26,29,30,33) without adjustment for alcohol drinking, summary RR for ever smokers was 2.70 (95% CI, 1.64–4.45), although heterogeneity was significant ($Q = 27.16$, $P < 0.001$).

There were several potential limitations in the Japanese studies reviewed here. One methodological issue was assessment of smoking exposures. Information on cigarette consumption was investigated by questionnaire in all cohort and case–control studies. However, the different categorization of smoking exposure was used in each questionnaire (e.g. smoking status, pack years, number of cigarettes a day). In addition, different definitions of smoking status were used. For example, former smokers with a short duration of smoking cessation were sometimes classified as current smokers. These might attenuate the association between cigarette smoking and esophageal cancer risk. In contrast, recall bias might intensify the association. The magnitude of the effects by these methodological issues may be small to influence the current observation.

Meta-analysis showed that ever smokers had significantly higher risk for esophageal cancer than never smokers. The asymmetrical appearance of the funnel plot and small P value for Egger's test suggested the existence of publication bias. Thus, summary RR of 3.01 might be overestimated. As the quantitative measurement of cigarette consumption was heterogeneous across studies, we could not see the dose–response relationships. The heterogeneity across studies is likely to be due to the different cigarette consumption levels by characteristics of subjects in each study, such as birth cohort, age, sex and base population. Moreover, only a little evidence was available about smoking cessation for esophageal cancer in Japanese population. Therefore, a pooled analysis using common cigarette consumption categories is warranted.

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

From these results, and on the bases of assumed biological plausibility, we conclude that there is convincing evidence that cigarette smoking strongly increases the risk of esophageal cancer in the Japanese population.

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

Author	Reference	Study period	Study population									
			Number of subjects for analysis, sex, age	Source of subjects	Event followed	Number of incident cases or deaths	Category	Number among cases	Relative risk (95% CI)	*P* value for trend	Confounding variables considered	Comments
Hirayama	21	1965–81	122 261 men	Population-based	Death	438 men	Smoking status			Not described	Age	Follow-up by death certificates, residential registry, 90% confidence intervals
			142 857 women				Non-smoker		1.0			
			≥40 years old				Daily smoker		2.24 (1.72–2.91)			
							Number of cigarettes/day					
							Non-smoker		1.0			
							1–9		1.62 (1.09–2.41)			
							10–19		2.04 (1.54–2.71)			
							≥20[a]		2.69 (2.05–3.53)			
							Age at start of smoking					
							Non-smoker		1.0			
							19 or below		1.61 (1.08–2.40)			
							20 or above		2.30 (1.76–3.00)			
							Years after smoking cessation					
							Non-smoker		1.0			
							1–4		1.53 (0.70–3.38)			
							5–9		1.13 (0.35–3.64)			
							≥10		1.96 (0.88–4.38)			
						147 women	Smoking status					
							Non-smoker		1			
							Daily smoker		1.75 (1.21–2.51)			
							Number of cigarettes/day					
							Non-smoker		1			
							1–9		1.74 (1.04–2.91)			
							10–19[a]		2.45 (1.53–3.93)			
							≥20		NA			
							Age at start of smoking					
							Non-smoker		1			
							19 or below		0			
							20 or above		1.83 (1.22–2.73)			
							Years after smoking cessation					
							Non-smoker		1			
							1–4		NA			
							5–9		NA			
							≥10		NA			

Sakata et al.	22	1988–99	46 465 men	Population-based	Death	100 men	Smoking status			Not described	Adjusted for age and centers
			40–79 years	45 areas in Japan			Non-smokers	7	1.0		
							Ex-smokers	25	2.71 (1.16–6.36)		
				JACC study			Smokers	68	4.36 (2.00–9.52)		
							Age at start of smoking			0.391	
							Non-smokers	7	1.0		
							25+	13	3.85 (1.54–9.64)		
							20–24	38	4.89 (1.98–12.07)		
							10–19	13	3.24 (1.06–9.89)		
							Cigarettes smoked per day			0.431	
							Non-smokers	7	1.0		
							1–10 cigarettes/day	15	5.11 (2.07–12.65)		
							11–20 cigarettes/day	39	4.42 (1.97–9.92)		
							21–30 cigarettes/day	8	3.19 (1.11–9.19)		
							≥30 cigarettes/day	5	4.33 (1.25–14.99)		
							Years of smoking			0.014	
							Non-smokers	7	1.0		
							≤25.0	4	2.05 (0.42–9.98)		
							25.1–35.0	13	3.54 (1.27–9.89)		
							35.1–45.0[a]	32	5.34 (2.32–12.30)		
							≥45.1	15	4.85 (1.62–14.53)		
							Cumulative amount of smoking			0.086	
							Non-smokers	7	1.0		
							1–19.9 PYs	6	3.24 (1.06–9.89)		
							20.0–29.9 PYs	16	4.89 (1.98–12.07)		
							30.0–39.9 PYs	14	3.85 (1.54–9.64)		
							≥40.0 PYs	28	4.86 (2.11–11.21)		
Ishikawa et al.	23	Cohort 1 1984–92	Cohort 1 9008 men	Population-based	Incidence	Cohort 1 38 cases	Cohort 1 Category of smoking			0.008	Adjusted for age, alcohol drinking, green tea, coffee and black tea
			≥40 years old	Miyagi pref.			Never	2	1.0		
		Cohort 2				Cohort 2	Former	6	2.49 (0.50–12.44)		
		1990–97	Cohort 2			40 cases	1–19 cigarettes/day	11	5.39 (1.18–24.61)		
			17 715 men				≥20 cigarettes/day	19	5.48 (1.24–24.18)		
			40–64 years								
							Cohort 2				
							Category of smoking			0.006	
							Never	2	1.0		
							Former	5	1.72 (0.33–8.92)		
							1–19 cigarettes/day	10	4.63 (1.01–21.30)		
							≥20 cigarettes/day	23	4.73 (1.10–20.34)		

Continued

Table 2. *Continued*

Author	Reference	Study period	Study population									
			Number of subjects for analysis, sex, age	Source of subjects	Event followed	Number of incident cases or deaths	Category	Number among cases	Relative risk (95% CI)	*P* value for trend	Confounding variables considered	Comments
							Pooled 1 and 2					
							Category of smoking			0.0001		
							Never	4	1.0			
							Former	11	2.07 (0.66–6.57)			
							1–19 cigarettes/day	21	5.00 (1.70–14.66)			
							≥20 cigarettes/day[a]	42	5.09 (1.80–14.40)			
Ishiguro et al.	24	Cohort 1	Cohort 1 + 2	Population-based	Incidence	Cohort 1 + 2	Cohort 1 + 2				Adjusted for age, area, BMI, preference of hot foods and drinks, ethanol consumption and flushing response	
		1990–2004	60 876 men	JPHC		215 cases	Smoking status					
		Cohort 2	≥40 years old				Never	14	1			
		1993–2004					Past	61	3.27 (1.78–5.99)			
							Current	140	3.69 (2.07–6.58)			
							Pack-years			0.001		
							<20	26	2.07 (1.07–4.00)			
							20–29	34	2.71 (1.44–5.11)			
							30–39	45	2.97 (1.61–5.48)			
							≥40[a]	95	4.81 (2.72–8.53)			
							Cigarettes/day among current smoker			0.001		
							<20	35	2.77 (1.43–5.34)			
							20–39	87	4.00 (2.21–7.22)			
							≥40	18	4.76 (2.31–9.81)			

NA, not available.
[a]Categories from which the magnitude of association was judged.

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

Author	Reference	Study period	Subjects				Category	Relative risk (95% CI)	*P* value for trend	Confounding variables considered	Comments
			Type and source	Definition	Number of cases	Number of controls					
Nakachi et al.	25	1973–85	Population-based	Cases: those who died of cancer of esophagus identified from death certificates Controls: those selected from Electoral Roll in the same area	343 (257 males and 86 females) (mean age: 68.3 male, 71.9 female)	343 (257 males and 86 females) (mean age: 68.2 male, 71.5 female)	Cumulative number of cigarettes Never <400 000 cigarettes ≥400 000 cigarettes[a]	 1.0 1.142 (0.685–1.904) 2.521 (1.230–5.166)	Not described	Matched for age, sex and neighborhood Not adjusted	
Sasaki et al.	26	1974–79	Hospital-based (three major hospitals in Nagoya and two in Wakayama)	Case: esophageal cancer patients who admitted to hospitals Controls: non-digestive tract cancer patients	201 (91 males and 28 females in Nagoya, 54 males and 28 females in Wakayama) (age not described)	403 (170 males and 86 females in Nagoya, 115 males and 61 females in Wakayama) (age not described)	Smoking status Nagoya (males) Non-smoker Smoker[a] Nagoya (females) Non-smoker Smoker Wakayama (males) Non-smoker Smoker Wakayama (females) Non-smoker Smoker[a]	 1.0 5.0 (2.1–11.8) 1.0 0.9 (0.3–2.6) 1.0 4.3 (1.7–11.3) 1.0 2.3 (0.8–6.8)	Not described	Matched for age, sex, hospital and time of admission Adjusted for age	
Hanaoka et al.	27	1989–91	Hospital-based (seven hospitals: Keio University, Iwate Medical College, Kurume University, Chiba University, National Shikoku Cancer Center, Aichi Cancer Center, Tokyo Women's Medical College)	Cases: male inpatients histologically diagnosed as having primary esophageal cancer Controls: male inpatients with diseases other than lung cancer, laryngeal cancer, hepatocellular carcinoma, pulmonary emphysema and chronic pancreatitis	141 (male only) (age not described)	141 (male only) (age not described) (90 with malignant neoplasms, 51 with benign diseases)	Tobacco consumption Never smoked Ex/light smoker Moderate smoker Moderate-to-heavy smoker[a] Heavy smoker	 1.0 1.24 (0.59–2.63) 1.41 (0.62–3.9) 1.52 (0.77–3.01) 1.03 (0.49–2.16)	0.55	Matched for age, sex and prefecture of residence Adjusted for alcohol consumption	Light smoker: <5 cigarettes/day, moderate smoker: 5≤cigarettes/day<15, moderate-to-heavy smoker: 15≤cigarettes/day<25, heavy smoker: ≥25 cigarettes/day
Takezaki et al.	28	1988–97	Hospital-based (Aichi Cancer Center Hospital)	Cases: first-visit male outpatients diagnosed as having primary cancer of esophagus Controls: first-visit male outpatients confirmed to be cancer-free	284 males (40–79 years old)	11 936 males (40–79 years old)	Smoking status Never Former Current[a] Number of cigarettes in current smokers Never 1–19/day ≥20/day Years of smoking in current smokers Never 1–29 ≥30 Age when started smoking in current smokers Never <20 years ≥20 years Years after quitting in former smokers Never 1–9 ≥10	 1.0 1.6 (0.9–2.8) 3.5 (2.1–5.8) 1.0 3.1 (1.8–5.5) 3.5 (2.1–5.9) 1.0 2.2 (1.1–4.4) 3.6 (2.1–6.0) 1.0 3.9 (2.2–6.9) 3.3 (1.9–5.5) 1.0 2.3 (1.3–4.2) 1.3 (0.7–2.3)	Not described	Not matched Adjusted for age, season of visit, drinking and consumption of raw vegetables	

Continued

Table 3. *Continued*

Author	Reference	Study period	Subjects				Category	Relative risk (95% CI)	*P* value for trend	Confounding variables considered	Comments
			Type and source	Definition	Number of cases	Number of controls					
Matsuo et al.	29	1999–2000	Hospital-based (Aichi Cancer Center Hospital)	Cases: outpatients first diagnosed as having esophageal cancer Controls: outpatients without a history of cancer	102 (86 males and 16 females) (40–76 years old)	241 (118 males and 123 females) (39–69 years old)	Smoking Never Former Current PYs ≤50 PYs >50[a]	 1.0 3.19 (1.34–7.58) 9.78 (4.49–21.3) 7.27 (3.17–16.7) 17.2 (6.61–44.7)	Not described	Adjusted for age and sex	
Tsuda et al.	30	1986–93	Population-based (Okayama Tobi area)	Cases: those who died with esophageal cancer identified by death certificates Controls: those who died with colon, pancreas, bladder and other urinary cancers	22 (age and sex not described)	198 (age and sex not described)	Smoking status Non-smoker Ex-smoker[a] Smoker	 1.0 6.59 (0.57–335.7) 3.50 (0.50–151.4)	Not described	Not adjusted	
Yokoyama et al.	31	2000–01	Hospital-based (National Cancer Center Hospital, National Cancer Center Hospital East, Kawasaki Municipal Hospital, National Osaka Hospital)	Cases: those with esophageal squamous cell carcinomas diagnosed by histology within 3 years of registration Controls: cancer-free males visited two Tokyo Clinics for annual health checkups	234 males (40–79 years old)	634 males (40–79 years old)	Smoking (pack-years) <30 ≥30[a]	 1.0 2.44 (1.55–3.84)	Not described	Not matched Adjusted for ALDH2, ADH2 and ADH3 genotypes, alcohol drinking, strong alcohol beverage, green-yellow vegetables and fruits	
Takagi et al.	32	1990–99	Hospital-based (Osaka Medical Center)	Cases: hospitalized female patients with esophageal cancer Controls: hospitalized female patients without cancer, benign tumor, cardiovascular disease and alcoholic liver disease	34 females (mean age: 63.4)	178 females (mean age: 53.1)	Smoking status Never Ever[a]	 1.0 1.7 (0.7–4.3)	Not described	Adjusted for age, alcohol drinking, hot food preference, tooth brushing	
Yokoyama et al.	33	2000–04	Hospital-based (National Cancer Center, National Cancer Center East, Kawasaki Municipal hospital, National Osaka Hospital)	Cases: female patients with esophageal squamous cell carcinoma within 3 years of their registration Controls: cancer-free females visited two clinics for annual health checkups	52 females (40–79 years old)	412 females (40–79 years old)	Smoking (pack-years) 0 <30 30+[a]	 1.0 3.89 (1.85–8.18) 5.12 (2.02–13.0)	0.0001	Adjusted for age	
Akiyama et al.	34	1997–2008	Hospital-based (Yokohama City University Hospital)	Cases: diagnosed as having esophageal squamous cell carcinoma Controls: patients who had undergone endoscopies as part of a health checkup	253 (225 males and 28 females) (38–86 years old)	254 (225 males and 28 females) (38–87 years old)	Smoking habit[a]	3.231 (2.062–5.063)	0.0001	Age/sex group matched	The detail of smoking habit was not described
Oze et al.	35	2001–05	Hospital-based (Aichi Cancer Center Hospital)	Cases: histologically confirmed esophageal cancer cases Controls: non-cancer first-visit outpatients at the same hospital	265 (235 males and 30 females) (33–79 years old)	530 (470 males and 60 females) (36–78 years old)	Pack-years PY < 5 5 ≤ PY < 20 20 ≤ PY < 40 PY ≥ 40[a]	 1.00 2.92 (1.31–6.50) 4.96 (2.51–9.81) 7.02 (3.58–13.77)	Not described	Age/sex matched Adjusted for alcohol consumption, ALDH2 genotype, fruit and vegetable intake, hot beverage intake, BMI	

[a]Categories from which the magnitude of association was judged.

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

Author	Study period	Study population					Category	Magnitude of association
		Sex	Number of subjects	Age range (years)	Event	Number of incident cases or deaths		
Hirayama	1965–81	Male	122 261	≥40	Death	438	Number of cigarettes/day	↑↑↑
		Female	142 857	≥40	Death	147	Number of cigarettes/day	↑↑
Sakata et al.	1988–99	Male	46 465	40–79	Death	100	Years of smoking	↑↑↑
Ishikawa et al.	Cohort 1 (1984–92)	Male	9008	≥40	Incidence	38	Category of smoking	↑↑↑
	Cohort 2 (1990–97)	Male	17 715	40–64	Incidence	40		
Ishiguro et al.	Cohort 1 (1993–2004)	Male	60 876	40–69	Incidence	215	Pack-years	↑↑↑
	Cohort 2 (1995–2004)							

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

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

Author	Study period	Study subjects				Category	Magnitude of association
		Sex	Age range (years)	Number of cases	Number of controls		
Nakachi et al.	1973–85	Male and female	Not specified	343 (M: 257, F: 86)	343 (M: 257, F: 86)	Cumulative number of cigarettes	↑↑↑
Sasaki et al.	1974–79	Male	Not specified	145	285	Smoking status	↑↑↑
		Female	Not specified	56	118	Smoking status	↑↑
Hanaoka et al.	1989–91	Male	Not specified	141	141	Tobacco consumption	↑
Takezaki et al.	1988–97	Male	40–79	346	11936	Smoking status	↑↑↑
Matsuo et al.	1999–2000	Male and female	40–76	102 (M: 86, F: 16)	241 (M: 118, F: 123)	Smoking	↑↑↑
Tsuda et al.	1986–93	Male and female	Not specified	22	98	Smoking status	↑↑
Yokoyama et al.	2000–01	Male	40–79	234	634	Smoking (pack-years)	↑↑↑
Takagi et al.	1990–99	Female	17–87	34	178	Smoking status	↑
Yokoyama et al.	2000–04	Female	40–79	52	412	Smoking (pack-years)	↑↑↑
Akiyama et al.	1997–2008	Male and female	38–86	265 (M: 235, F: 30)	530 (M: 470, F: 60)	Smoking habit	↑↑↑
Oze et al.	2001–05	Male and female	33–79	742 (M: 641, F: 101)	820 (M: 506, F: 314)	Pack-years	↑↑↑

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

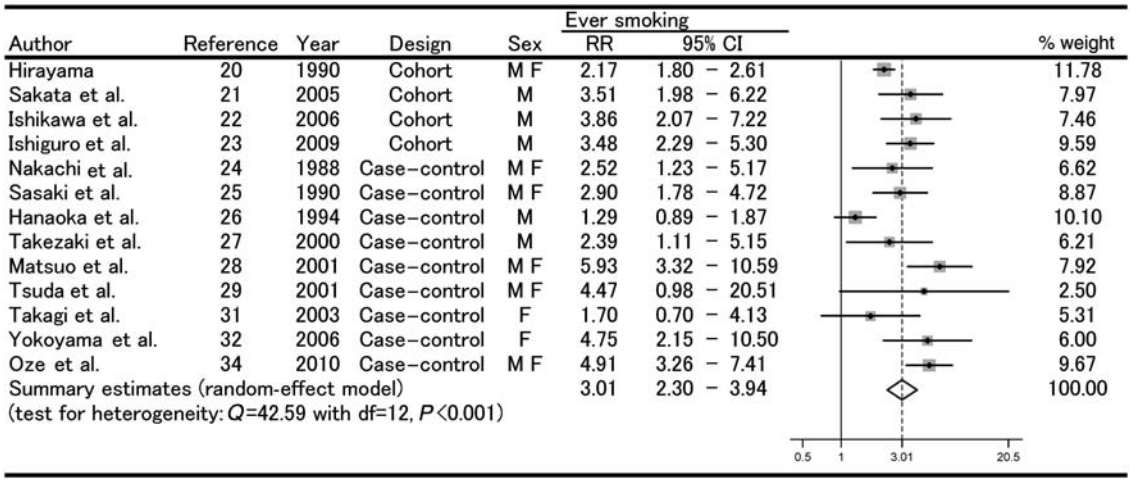

Figure 1. Summary estimates of the association between cigarette smoking and esophageal cancer risk. RR, relative risk; M, male; F, female. The boxed area represents the contribution of each study (weight) to the meta-analysis.

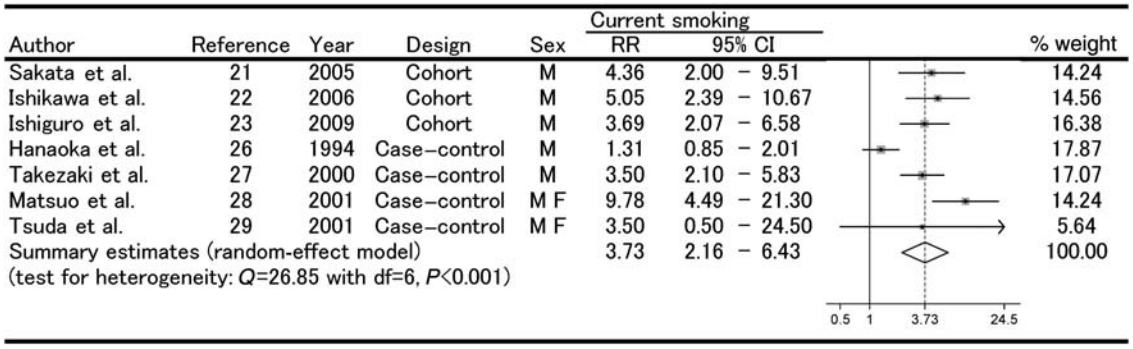

Figure 2. Summary estimates of the association between cigarette smoking and esophageal cancer risk. RR, relative risk; M, male; F, female. The boxed area represents the contribution of each study (weight) to the meta-analysis.

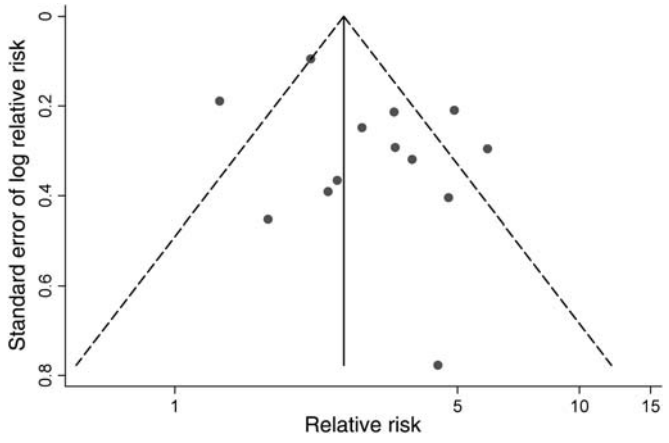

Figure 3. Funnel plot with 95% confidence limits.

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Conflict of interest statement

None declared.

References

1. U.S. Department of Health and Human Services. *How Tobacco Smoke Causes Disease: the Biology and Behavioral Basis for Smoking-attributable Disease: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.
2. World Health Organization/International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Smokeless Tobacco and Some Tobacco-specific* N-*nitrosamines*. Lyon, France: WHO Press, 2004.

3. World Health Organization/International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Tobacco Smoke and Involuntary Smoking*. Lyon, France: WHO Press, 2004.
4. Botterweck AA, Schouten LJ, Volovics A, Dorant E, van Den Brandt PA. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. *Int J Epidemiol* 2000;29:645–54.
5. Corley DA, Buffler PA. Oesophageal and gastric cardia adenocarcinomas: analysis of regional variation using the Cancer Incidence in Five Continents database. *Int J Epidemiol* 2001;30:1415–25.
6. Fernandes ML, Seow A, Chan YH, Ho KY. Opposing trends in incidence of esophageal squamous cell carcinoma and adenocarcinoma in a multi-ethnic Asian country. *Am J Gastroenterol* 2006;101:1430–6.
7. Shibata A, Matsuda T, Ajiki W, Sobue T. Trend in incidence of adenocarcinoma of the esophagus in Japan, 1993–2001. *Jpn J Clin Oncol* 2008;38:464–8.
8. Inoue M, Tsuji I, Wakai K, Nagata C, Mizoue T, Tanaka K, et al. Evaluation based on systematic review of epidemiological evidence among Japanese populations: tobacco smoking and total cancer risk. *Jpn J Clin Oncol* 2005;35:404–11.
9. Mizoue T, Inoue M, Tanaka K, Tsuji I, Wakai K, Nagata C, et al. Tobacco smoking and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* 2006;36:25–39.
10. Nagata C, Mizoue T, Tanaka K, Tsuji I, Wakai K, Inoue M, et al. Tobacco smoking and breast cancer risk: an evaluation based on a systematic review of epidemiological evidence among the Japanese population. *Jpn J Clin Oncol* 2006;36:387–94.
11. Nishino Y, Inoue M, Tsuji I, Wakai K, Nagata C, Mizoue T, et al. Tobacco smoking and gastric cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* 2006;36:800–07.
12. Tanaka K, Tsuji I, Wakai K, Nagata C, Mizoue T, Inoue M, et al. Cigarette smoking and liver cancer risk: an evaluation based on a systematic review of epidemiologic evidence among Japanese. *Jpn J Clin Oncol* 2006;36:445–56.
13. 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.
14. Oze I, Matsuo K, Wakai K, Nagata C, Mizoue T, Tanaka K, et al. Alcohol drinking and esophageal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* 2011;41:677–92.
15. World Health Organization. *WHO Technical Reports Series 916. Diet, Nutrition and Prevention of Chronic Diseases: Report of a Joint WHO/FAO Expert Consultation*. Geneva: WHO, 2003.
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
17. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–101.
18. Akiba S, Hirayama T. Cigarette smoking and cancer mortality risk in Japanese men and women—results from reanalysis of the six-prefecture cohort study data. *Environ Health Perspect* 1990;87:19–26.
19. Kinjo Y, Cui Y, Akiba S, Watanabe S, Yamaguchi N, Sobue T, et al. Mortality risks of oesophageal cancer associated with hot tea, alcohol, tobacco and diet in Japan. *J Epidemiol/Jpn Epidemiol Assoc* 1998;8:235–43.
20. Yang CX, Matsuo K, Ito H, Hirose K, Wakai K, Saito T, et al. Esophageal cancer risk by ALDH2 and ADH2 polymorphisms and alcohol consumption: exploration of gene–environment and gene–gene interactions. *Asian Pac J Cancer Prev* 2005;6:256–62.
21. Hirayama T. *Life-style and Mortality. A Large-scale Census-based Cohort Study in Japan*. Basel, Switzerland: Karger, 1990.
22. Sakata K, Hoshiyama Y, Morioka S, Hashimoto T, Takeshita T, Tamakoshi A. Smoking, alcohol drinking and esophageal cancer: findings from the JACC Study. *J Epidemiol/Jpn Epidemiol Assoc* 2005;15:S212–9.
23. Ishikawa A, Kuriyama S, Tsubono Y, Fukao A, Takahashi H, Tachiya H, et al. Smoking, alcohol drinking, green tea consumption and the risk of esophageal cancer in Japanese men. *J Epidemiol/Jpn Epidemiol Assoc* 2006;16:185–92.
24. Ishiguro S, Sasazuki S, Inoue M, Kurahashi N, Iwasaki M, Tsugane S. Effect of alcohol consumption, cigarette smoking and flushing response on esophageal cancer risk: a population-based cohort study (JPHC study). *Cancer Lett* 2009;275:240–6.
25. Nakachi K, Imai K, Hoshiyama Y, Sasaba T. The joint effects of two factors in the aetiology of oesophageal cancer in Japan. *J Epidemiol Commun Health* 1988;42:355–64.
26. Sasaki R, Aoki K, Takeda S. Contribution of dietary habits to esophageal cancer in Japan. *Prog Clin Biol Res* 1990;346:83–92.
27. Hanaoka T, Tsugane S, Ando N, Ishida K, Kakegawa T, Isono K, et al. Alcohol consumption and risk of esophageal cancer in Japan: a case-control study in seven hospitals. *Jpn J Clin Oncol* 1994;24:241–6.
28. Takezaki T, Shinoda M, Hatooka S, Hasegawa Y, Nakamura S, Hirose K, et al. Subsite-specific risk factors for hypopharyngeal and esophageal cancer (Japan). *Cancer Causes Control* 2000;11:597–608.
29. Matsuo K, Hamajima N, Shinoda M, Hatooka S, Inoue M, Takezaki T, et al. Gene-environment interaction between an aldehyde dehydrogenase-2 (ALDH2) polymorphism and alcohol consumption for the risk of esophageal cancer. *Carcinogenesis* 2001;22:913–6.
30. Tsuda T, Mino Y, Babazono A, Shigemi J, Otsu T, Yamamoto E. A case–control study of the relationships among silica exposure, gastric cancer, and esophageal cancer. *Am J Ind Med* 2001;39:52–7.
31. Yokoyama A, Kato H, Yokoyama T, Tsujinaka T, Muto M, Omori T, et al. Genetic polymorphisms of alcohol and aldehyde dehydrogenases and glutathione *S*-transferase M1 and drinking, smoking, and diet in Japanese men with esophageal squamous cell carcinoma. *Carcinogenesis* 2002;23:1851–9.
32. Takagi A, Ajiki W, Tsukuma H. A case–control study to identify risk factors for female esophageal cancer in Osaka prefecture. *Kousei no Shihyou* 2003;50:33–8 (in Japanese).
33. Yokoyama A, Kato H, Yokoyama T, Igaki H, Tsujinaka T, Muto M, et al. Esophageal squamous cell carcinoma and aldehyde dehydrogenase-2 genotypes in Japanese females. *Alcohol Clin Exp Res* 2006;30:491–500.
34. Akiyama T, Inamori M, Iida H, Endo H, Hosono K, Yoneda K, et al. Macroscopic extent of gastric mucosal atrophy: increased risk factor for esophageal squamous cell carcinoma in Japan. *BMC Gastroenterol* 2009;9:34.
35. Oze I, Matsuo K, Hosono S, Ito H, Kawase T, Watanabe M, et al. Comparison between self-reported facial flushing after alcohol consumption and ALDH2 Glu504Lys polymorphism for risk of upper aerodigestive tract cancer in a Japanese population. *Cancer Sci* 2010;101:1875–80.

Appendix

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