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Tobacco Smoking and Gastric Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence among the Japanese Population

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Background: We evaluated the association between tobacco smoking and gastric cancer risk among the Japanese population based on a systematic review of epidemiologic evidence.
Methods: Original data were collected by searches of MEDLINE using PubMed, complemented with manual searches. Evaluation of associations was based on the strength of evidence and the magnitude of association, together with biological plausibility, as evaluated previously by the International Agency for Research on Cancer.
Results: Ten cohort studies and 16 case-control studies were identified. In men, most studies reported moderate or strong positive associations between smoking and gastric cancer. In women, the positive association was weaker than in men. Of eight studies (three cohort studies and five case–case control studies), two cohort and three case control studies reported a weakly to strongly increased risk of gastric cancer. The summary relative risk for current smokers was estimated to be 1.56 (95% confidence intervals 1.36–1.80), 1.79 (1.51–2.12), 1.22 (1.07–1.38) for the total population, men and women, respectively.
Conclusion: We conclude that there is convincing evidence that tobacco smoking moderately increases the risk of gastric cancer among the Japanese population.

Key words: systematic review – epidemiology – tobacco smoking – stomach cancer – Japanese

INTRODUCTION

Gastric cancer is still the most common cancer in Japan (1). Therefore, its prevention is one of the most important targets for cancer control.

The International Agency for Research on Cancer (IARC) concluded in 2002 that there was 'sufficient' evidence of causality between tobacco smoking and gastric cancer (2). This causality would have public health significance in Japan, where the smoking rate in men is one of the highest in the world. However, it may be premature to draw a conclusion about the association between tobacco smoking and gastric cancer in Japan, because the prevalence of risk factors such as *Helicobacter pylori* infection and salt intake in the Japanese differs from that in other countries. Also the Japanese have different genetic and environmental factors which might modify the association between smoking and the risk of gastric cancer from people of other countries. Therefore, it is necessary that the association between smoking and the risk of gastric cancer in the Japanese

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population is evaluated on the basis of previous Japanese epidemiologic studies. In addition, after the IARC conclusion, important findings about the association between smoking and gastric cancer from large-scale prospective studies in Japan were reported.

The aim of this study was to review epidemiological findings on the association between tobacco smoking and gastric cancer among the Japanese population. The findings are summarized and the magnitude of the effect is evaluated. This study was conducted as part of a systematic review of epidemiological evidence regarding lifestyle and cancer in the Japanese population (3).

METHODS

Original data for this review were collected by searches of MEDLINE using Pub Med, complemented by manual searches of references from relevant articles when necessary. All epidemiological studies on the association between tobacco smoking and gastric cancer incidence or mortality among Japanese from January 1966 to March 2005, including papers in press if available, were identified using the search terms 'tobacco smoking', 'gastric cancer', 'stomach cancer', 'cohort studies', 'case-control studies', 'Japan' and 'Japanese' as key words found in the abstract. Papers written in 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 by study design as cohort or case-control studies. In the case of multiple publications of analyses of the same or overlapping datasets, only data from the largest or the most recent results were included, and incidence was given priority over mortality as an outcome measure. Incidence was also given priority in a single publication describing both incidence and mortality.

Evaluation was made based on the strength of evidence and the magnitude of association. First, the relative risks in each epidemiological study were grouped by magnitude of association with consideration to statistical significance (SS) or no statistical significance (NS), as strong, <0.5 or >2.0 (SS); moderate, either (i) <0.5 or >2.0 (NS), (ii) 1.5–2 (SS) or (iii) 0.5–0.67 (SS); weak, either (i) 1.5–2 (NS), (ii) 0.5–0.67 (NS) or (iii) 0.67–1.5 (SS); or no association, 0.67–1.5 (NS). After this process, the strength of evidence was evaluated in a similar manner to that used by the WHO/FAO Expert Consultation Group in which evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient' (4). We assumed that biological plausibility corresponded to the judgment of the most recent evaluation from the IARC (2). Notwithstanding the use of this quantitative assessment rule, arbitrary assessment cannot be avoided when considerable variation in the magnitude of association existed between the results of the study. The final judgment, therefore, was made based on the consensus of research group members and thus was not necessarily objective.

In addition, when we reached a conclusion that there was 'convincing' or 'probable' evidence of a positive or inverse association, a meta-analysis was conducted to obtain summary estimates of the association. In general, studies which reported relative risks and their confidence intervals (CIs) by comparing current smokers with never-smokers were included in the meta-analysis, but for those which categorized risk values separately according to smoking amount, such as the number of cigarettes smoked or pack-year index, meta-analysis was conducted to estimate summary risk values for current smokers, and these values were then used for further 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 estimated by testing the Q statistic, with the model used to determine summary relative risk and its 95% CI, namely a random or fixed effect model, selected according to the statistical significance in the Q statistic. Meta-analysis was done using the meta command of STATA statistical package (5).

MAIN FEATURES AND COMMENTS

A total of 10 cohort studies and 16 case-control studies were identified (Table 1 and Table 2 respectively; these tables are available as supplementary data at http://jjco.oxfordjournals.org). Among the cohort studies, four presented results by gender (7,9,13,15) four for men only (6,11,12,14), and two for men and women combined (8,10). As for the case-control studies, the number of those that presented results by gender, for men only, for women only, and for men and women combined were seven (19–21,24,27,28,30) four (16,17,25,26), one (29) and four (18,22,23,31), respectively. After excluding one case-control study (20) owing to the unavailability of a point estimate or *P* value, two cohort (8,13) and two case-control studies (24,26) because of a shorter study analysis period than another study of the same population, and one cohort (11) and one case-control study (29) because subgroups of the same dataset as those used in another study were employed, we obtained a summary of the magnitude of association for the remaining studies in Table 3 and Table 4 for cohort studies and case-control studies, respectively.

All of six studies (6,7,9,12,14,15) presenting relative risks for gastric cancer in male current smokers reported a significant risk increase among the current smokers. The magnitude of increased risk was reported as strong by one study (9), moderate by three studies (6,12,14) and weak by two studies (7,15). The study of men and women combined (10) found a non-significantly increased risk of gastric cancer in subjects who smoked 20 cigarettes or over per day. The increased risk in women was weaker than in men; two

Table 3. Summary of the association between tobacco smoking and gastric cancer risk, cohort study

References			Study period	Study subjects					Magnitude of association
Author	Year	(Ref. No.)		Sex	No. of subjects	Ranged age	Event	Number of incident cases or deaths	
Kono S	1987	(6)	1965–1983	Men	5130	27–89	Death	116	↑↑
Hirayama T	1990	(7)	1966–1982	Men	122 261	≥40	Death	3,414	↑
				Women	142 857	≥40	Death	1,833	↑
Kato I	1992	(9)	1985–1991	Men	9753 (total)	≥40	Death	35	↑↑↑
				Women		≥30	Death	22	↑
Inoue M	1996	(10)	1985–1995	Men and women	5373	Not specified	Incidence	69	↑
Sasazuki S	2002	(12)	1990–1999	Men	19 657	40–59	Incidence	293	↑↑
Koizumi Y	2004	(14)	1984–1992	Men	9980	≥40	Incidence	228	↑↑*
			1990–1997	Men	19 412	40–64	Incidence	223	
Fujino Y	2005	(15)	1988–1999	Men	43 482	40–79	Death	522	↑
				Women	54 480	40–79	Death	235	–

↑↑↑, strongly positive; ↑↑, moderately positive; ↑, weakly positive; –, no association.
* The magnitude of association was evaluated on the results from a pooled analysis of two cohort studies.

Table 4. Summary of the association between tobacco smoking and gastric cancer risk, case-control study

References			Study period	Study subjects				Magnitude of association
Author	Year	(Ref. No.)		Sex	Ranged age	Number of cases	Number of controls	
Haenzel W	1976	(16)	1962–1964 (Hiroshima)	Men	Not specified	247 (Hiroshima)	494 (Hiroshima)	–
			1962–1965 (Miyagi)	Men	Not specified	279 (Miyagi)	558 (Miyagi)	–
Tajima K	1985	(17)	1981–1984	Men	40–70	59	111	↑↑
Hoshino H	1985	(18)	1979–1982	Men and women	Not specified	460	460	↑↑↑
Kono S	1988	(19)	1979–1982	Men	20–75	74	Hospital controls 1171	↑ (Hospital controls)
							Population controls 148	↑(Population controls)
				Women	20–75	65	Hospital controls 1403	– (Hospital controls)
							Population controls 130	– (Population controls)
Kato I	1990	(21)	1985–1989	Men	Not specified	289	1247	↑↑↑
				Women	Not specified	138	1767	↑
Tominaga K	1991	(22)	1971–1985	Men and women	Not specified	294 (188 men, 106 women)	588 (376 men, 212 women)	↑↑↑
Hoshiyama Y	1992	(23)	1984–1990	Men and women	Not specified	294 (206 men, 88 women)	Hospital controls 202	– (Hospital controls)
							Population controls 294	– (Population controls)
Murata M	1996	(25)	1984–1993	Men	Not specified	246	493	–
Inoue M	1999	(27)	1988–1995	Men	Not specified	651	12 041	↑↑↑
				Women	Not specified	344	31 805	↑↑
Kikuchi S	2002	(28)	1993–1995	Men	≤69	494	448	↑↑↑
				Women	≤69	224	435	↑↑↑
Minami Y	2003	(30)	1997–2001	Men	≥40	429	1222	↑↑
				Women	≥40	185	1222	–
Machida-Montani A	2004	(31)	1998–2002	Men and women	20–74 (cases)	122 (non-cardia cases only)	235	↑↑↑

↑↑↑, strongly positive; ↑↑, moderately positive; ↑, weakly positive; −, no association.

studies (7,9) reported a weakly increased risk and another reported no association (15).

Among eight case-control studies presenting results for men, three (21,27,28) presented strongly, two (17,30) presented moderately, and one (19) presented weakly increased risks of gastric cancer in current or ever smokers compared with never smokers. In the remaining two studies (16,25), no association was observed. Of the case-control studies with men and women combined, three (18,22,31) reported a strongly increased risk of gastric cancer, and one reported no association (23). In women, two studies (27,28) showed a strongly or moderately increased risk of gastric cancer, and *P* for trend was statistically significant in both of them. One study (21) reported a non-significant weakly increased risk in subjects smoking >20 cigarettes per day and the remaining two studies (19,30) showed no association.

The summary relative risk (RR) for current smokers estimated by meta-analysis is presented in Fig. 1. In the meta-analysis, five case-control studies (16–19,25) were excluded owing to unavailability of the CIs, one cohort study (6) because of the inclusion of ex-smokers in reference category and two case control studies (22,28) because there was no report on the RR for current smokers. For men, the RR was 1.49 (95% CI 1.37–1.62) in cohort studies, 2.20 (1.84–2.62) in case-control studies, and 1.79 (1.51–2.12) in all studies. The corresponding RR for women was 1.16 (1.01–1.34), 1.16 (0.66–2.05) and 1.22 (1.07–1.38), respectively. The result of meta-analysis for men and women combined also showed a significantly elevated summary RR for cohort, case-control and all studies.

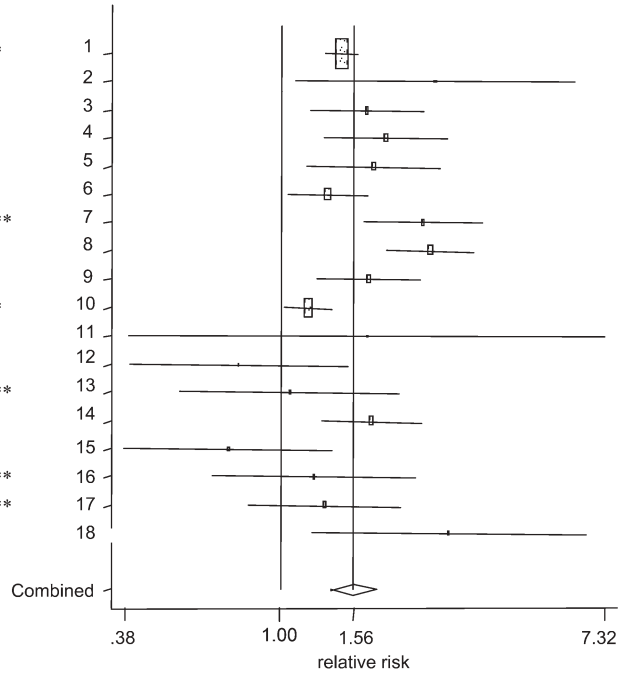
Overall, most epidemiologic studies consistently presented a statistically significant risk elevation for gastric cancer in male smokers. The results for female smokers were less consistent, five of eight epidemiologic studies showing a weakly to strongly increased risk of gastric cancer. Although the summary relative risk was elevated regardless of sex and study design, the risk was higher for case-control studies than for cohort studies and for men than for women. In case-control studies, health-conscious people might be more likely to be selected as controls especially in cases where participants in health check-ups were used as controls, and patients with gastric cancer might be more likely to report their smoking histories than controls. This selection and recall bias might lead to overestimation of the association between smoking and gastric cancer risk. One of the reasons why summary estimates of the association between tobacco smoking and gastric cancer risk for men were higher than for women was considered to be the difference in the cumulative amount of cigarettes smoked. It is not clear, however, whether there is a gender difference in susceptibility to tobacco smoking from the results of the strength of association by the stratum of amount of cigarettes smoked.

Dietary factors might be potential confounders between tobacco smoking and gastric cancer. In particular, high salt intake is an important risk factor for gastric cancer in the Japanese, who consume more salt than Westerners. Among previous studies conducted on Japanese populations, only three cohort (12,14,15) and three case-control studies (21,23,27) were adjusted for intake of salty food such as pickled vegetables or a preference for salty food. In one case-control study (23), a positive association between tobacco smoking and gastric cancer risk diminished substantially after adjustment for preference for salty foods, miso soup and pickled vegetables. However, the results of two cohort (14,15) and one case-control (21) studies were not changed substantially after multivariate-adjusted analyses. The other studies (12,27) reported only the results of multivariate-adjusted analysis, which presented a moderate to strong positive association between tobacco smoking and gastric cancer. Total consumption of salt was evaluated in only one case-control study (31). The adjusted odds ratio of gastric cancer for current smokers in this study was 2.8 (95% CI, 1.2–6.5).

In 1994, the IARC recognized *H. pylori* as a class 1 human carcinogen. *H. pylori* is an established risk factor for gastric cancer and might be one of the potential confounders between tobacco smoking and gastric cancer. No cohort study has evaluated *H. pylori* infection status and only two case-control studies (28,31) reported the odds ratio adjusted for *H. pylori* infection. A case-control study conducted in Metropolitan Tokyo (28) presented a linear association between smoking dose (cigarette–years) and the risk of stomach cancer in males and an elevated risk in 400+ cigarette–years females, even after adjustment for *H. pylori* infection. A multi-center, hospital-based case-control study in Nagano (31) reported that smoking was associated with an increased risk of non-cardia gastric cancer among both *H. pylori*-positive and -negative subjects, and that there was no statistically significant interaction between smoking and *H. pylori* infection. These studies suggested that smoking was a risk factor of gastric cancer independent of *H. pylori* infection. In addition, most studies investigating the association between *H. pylori* infection status and smoking habit in Japan presented no association (32–36) or lower prevalence of *H. pylori* infection in current smokers than in never-smokers (37,38), except for one study which reported that smoking was positively associated with *H. pylori* infection among male outpatients who underwent gastroscopy (39). Therefore, a positive association between smoking and the risk of gastric cancer is not likely to be brought about by the confounding effect of *H. pylori* infection.

Several studies (12,14,24,28,29) investigated the effect of smoking on gastric cancer according to anatomic subsites. The results of two cohort studies were not consistent. The JPHC study (12) reported an increased risk of cardia cancer and differentiated-type distal cancer for current smokers, whereas no relationship with undifferentiated-type distal cancer was found. However, a pooled analysis of two prospective studies in Miyagi (14) revealed a significantly increased risk associated with smoking only in the antrum but not in the cardia or body. A case-control study conducted

No.	Study Author	Ref.	(Year)	Sex	Design	event	Current smokers RR	(95%CI)	
1	Hirayama T	7	(1990)	M	CH	Death	1.45	(1.31- 1.60)	*
2	Kato I	9	(1992)	M	CH	Incidence	2.58	(1.09- 6.10)	
3	Sasazuki S	12	(2002)	M	CH	Incidence	1.70	(1.20- 2.40)	
4	Koizumi Y	14	(2004)	M	CH	Incidence	1.91	(1.31- 2.79)	
5	Koizumi Y	14	(2004)	M	CH	Incidence	1.76	(1.17- 2.66)	
6	Fujino Y	15	(2005)	M	CH	Death	1.33	(1.04- 1.70)	
7	Kato I	21	(1990)	M	CC		2.40	(1.67- 3.45)	**
8	Inoue M	27	(1999)	M	CC		2.50	(1.91- 3.27)	
9	Minami Y	30	(2003)	M	CC		1.71	(1.25- 2.36)	
10	Hirayama T	7	(1990)	W	CH	Death	1.18	(1.02- 1.37)	*
11	Kato I	9	(1992)	W	CH	Death	1.69	(0.39- 7.31)	
12	Fujino Y	15	(2005)	W	CH	Death	0.77	(0.39- 1.50)	
13	Kato I	21	(1990)	W	CC		1.06	(0.54- 2.08)	**
14	Inoue M	27	(1999)	W	CC		1.74	(1.28- 2.36)	
15	Minami Y	30	(2003)	W	CC		0.72	(0.38- 1.37)	
16	Inoue M	10	(1996)	MW	CH	Death	1.22	(0.65- 2.29)	**
17	Hoshiyama Y	23	(1992)	MW	CC		1.31	(0.82- 2.09)	**
18	Machida-Montani A	31	(2004)	MW	CC		2.80	(1.20- 6.50)	



Summary estimates: Men		Total	1.79 (1.51- 2.12)	(Random effect model; Test for heterogeneity: Q=23.792 with df=8, p=0.002)
		Cohort studies	1.49 (1.37- 1.62)	(Fixed effect model; Test for heterogeneity: Q=5.513 with df=5, p=0.357)
		Case-control studies	2.20 (1.84- 2.62)	(Fixed effect model; Test for heterogeneity: Q=3.501 with df=2, p=0.174)
	Women	Total	1.22 (1.07- 1.38)	(Fixed effect model; Test for heterogeneity: Q=10.126 with df=5, p=0.072)
		Cohort studies	1.16 (1.01- 1.34)	(Fixed effect model; Test for heterogeneity: Q=1.727 with df=2, p=0.422)
		Case-control studies	1.16 (0.66- 2.05)	(Random effect model; Test for heterogeneity: Q=6.738 with df=2, p=0.034)
	Total	Total	1.56 (1.36- 1.80)	(Random effect model; Test for heterogeneity: Q=50.153 with df=17, p<0.001)
		Cohort studies	1.39 (1.30- 1.50)	(Fixed effect model; Test for heterogeneity: Q=15.985 with df=9, p=0.067)
		Case-control studies	1.70 (1.31- 2.21)	(Random effect model; Test for heterogeneity: Q=21.178 with df=7, p=0.004)

RR: Relative risk, CH: cohort study, CC: case-control study, NA: not available, M: men, W: women
The boxed area represents the contribution of each study (weight) to the meta-analysis.
*95%CI of reference (7) was estimated from the RR and 90%CI given.
**RR and 95%CI of reference (10), (21), and (23) was estimated from those estimated for daily amount of smoking categories by meta-analysis.
References (16-20) and (25) were excluded from the meta-analysis since point estimate and/or confidence intervals were not available or unble to estimate from other given values.
References (8), (13), (24) and (26) was excluded from the meta-analysis due to shorter study period in the reports from the same population.
References (11) and (29) was excluded from the meta-analysis due to subgroup in the reports from the same population
Reference (6) was excluded from the meta-analysis due to the inclusion of ex-smokers in reference category.
References (22) and (28) was excluded from the meta-analysis due to no report on the RR for current smokers.

Figure 1. Summary estimates of the association between tobacco smoking and gastric cancer risk.

at Aichi Cancer Center showed that habitual smoking increased the risk of cardia cancer more prominently in men (24), and less prominently in postmenopausal women (29). Another case-control study in Metropolitan Tokyo (28) concluded that ever smokers had consistently elevated risks for all subsites of gastric cancer, but that the odds ratio for middle cancer was slightly lower than that for proximal and distal cancers. Therefore, it is not clear whether the effect of smoking differs among anatomical subsites. Also, it has been hypothesized that differentiated-type gastric cancer may be more affected by environmental factors than the undifferentiated type, and several studies (12,14,21,27,28,29) have investigated the effect of smoking on the risk of gastric cancer in relation to histologic type. However, there was no clear difference in risk pattern according to histologic subtype except for distal gastric cancer in the JPHC study (12).

A meta-analysis published in 1997 (40), including studies conducted in Japan and overseas, presented summary estimates weighted on both the number of cases and the inverse variance of risk. The results of the analysis weighted on the number of cases showed a higher summary relative risk in men (RR = 1.59) than in women (RR = 1.11) for ever smokers. The summary variance-weighted relative risk was calculated only for men because only one study provided confidence limits for women. The result was 1.44 and 1.47 for ever and current smokers, respectively. The results of large-scale cohort studies in the USA (41) and Europe (42), published after the meta-analysis in 1997, also showed cigarette smokers were at significantly higher risk of gastric cancer. The IARC evaluated the carcinogenic effects of tobacco smoking on various sites in a recent report and concluded that there is sufficient evidence of carcinogenicity in humans that smoking causes gastric cancer (2).

EVALUATION OF EVIDENCE ON TOBACCO SMOKING AND GASTRIC CANCER RISK IN JAPANESE

From these results and assumed biological plausibility, we conclude that there is convincing evidence that tobacco smoking moderately increases the risk of gastric cancer among the Japanese population. As few previous studies have made sufficient adjustment for important potential confounding factors such as salt intake and *H. pylori* infection, the extent of any confounding effect is unclear. However, evidence currently available suggests that these factors are unlikely to exert a strong confounding effect.

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