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Evaluation Based on Systematic Review of Epidemiological Evidence Among Japanese Populations: Tobacco Smoking and Total Cancer Risk

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Background: We evaluated the association between tobacco smoking and total cancer risk among Japanese populations based on a systematic review of epidemiological evidence.
Methods: Original data were obtained from 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 previously evaluated by the International Agency for Research on Cancer. Meta-analysis of associations was also conducted to obtain summary estimates of association.
Results: A total of eight cohort studies were identified. In men, all studies consistently showed a moderately increased risk of total cancer in current smokers compared with never-smokers. In women, an increase in risk was seen but was weaker than in men. The summary relative risk was estimated as 1.53 (95% confidence interval 1.41–1.65).
Conclusion: We conclude that there is convincing evidence that current tobacco smoking moderately increases the risk (≈1.5 times) of total cancer in the Japanese population compared with never-smoking Japanese.

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

INTRODUCTION

In Japan, lifestyle-related diseases such as cancer have been recognized as major components of the overall pattern of disease for decades, and the importance of the prevention of cancer by lifestyle modification is now strongly acknowledged. Various international and domestic guidelines and recommendations based on the epidemiological evidence for cancer prevention have appeared, with notable examples from the International Agency for Research on Cancer (IARC) (1), World Cancer Research Fund and American Institute for Cancer Research (2), World Health Organization and Food and Agriculture Organization (WHO/FAO) (3) and Harvard Center for Cancer Prevention (4). Evidence for these has for the most part been derived from Western populations, ensuring their suitability for these populations. Given that the host and environmental factors of Japanese populations are not always the same as those of the West, however, these guidelines may be incompletely relevant to Japanese. It is therefore important to evaluate the existing epidemiological evidence derived from Japanese populations, and from these derive relevant recommendations regarding major risk factors of cancer applicable to Japanese.

Our research group has investigated the association between health-related lifestyles and total cancers, as well as the five major cancer sites in Japan, namely the stomach, colon and rectum, liver, lung and breast. Findings were summarized and the magnitude of the effect of each lifestyle on cancer was assessed based on previous publications targeting Japanese populations. The present study focuses on the association between tobacco smoking and total cancer risk among Japanese populations.

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METHODS

Original data for this review were identified by searches of MEDLINE using PubMed, complemented by manual searches of references from relevant articles where necessary. All epidemiological studies on the association between tobacco smoking and total cancer incidence or mortality among Japanese from 1966 to 2004, including papers in press if available, were identified using the search terms 'tobacco smoking', 'cancer', 'risk', 'cohort study', 'case–control study' and 'Japan' as keywords found in the abstract. Papers written in either English or Japanese were reviewed, and only studies on Japanese populations living in Japan were included. Individual results were summarized in the tables separately by study design as cohort or case–control studies.

Evaluation was made based on the strength of evidence and the magnitude of association. First, relative risks in each epidemiological study were grouped by magnitude of association, with consideration of 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 to <0.67 (SS); weak, either (i) >1.5–2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association, 0.67–1.5 (NS). Criteria for the magnitude of association are summarized in Table 1. After this process, overall magnitude of association was judged using the same criteria as for magnitude of association, together with the strength of evidence in a similar manner to that used in the WHO/FAO Expert Consultation Report (3), in which evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient' (Table 2). We assumed that biological plausibility corresponded to the judgment of the most recent evaluation from the IARC (1). Notwithstanding the use of this quantitative assessment rule, arbitrary assessment cannot be avoided when there is considerable variation in the magnitude of association between the results of each study. The final judgment, therefore, is made based on the consensus of research group members, and is not necessarily objective.

In addition, when there was 'convincing' or 'probable' evidence of a positive or inverse association, 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. In the case of multiple publication of analyses of the same or overlapping data sets, only data from the largest or most updated results were included, and incidence was given priority over mortality as an outcome measure. Incidence was also given priority in single publications describing both incidence and mortality. 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, 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 version 8 (13).

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. Evaluation of the strength of epidemiological evidence in the present report

Strength of evidence*	Description
Convincing	Evidence based on epidemiological studies showing consistent associations between exposure and disease, with little or no evidence to the contrary. The available evidence is based on a substantial number of studies. The association should be biologically plausible.
Probable	Evidence based on epidemiological studies showing fairly consistent associations between exposure and disease, but where perceived shortcomings in the available evidence or some evidence to the contrary preclude a more definite judgment. Shortcomings in the evidence may be any of the following: insufficient duration of studies; insufficient studies available; inadequate sample sizes; or incomplete follow-up. Laboratory evidence is usually supportive, and the association should be biologically plausible.
Possible	Evidence based mainly on findings from case–control and cross-sectional studies. Insufficient observational studies are available. Evidence based on non-epidemiological studies, such as clinical and laboratory investigations, is supportive. More studies are required to support the tentative associations, which should also be biologically plausible.
Insufficient	Evidence based on findings of a few studies which are suggestive, but are insufficient to establish an association between exposure and disease. More well-designed research is required to support the tentative associations.

*Criteria for the strength of evidence are based on those used in the Report of a Joint WHO/FAO Expert Consultation (3).

Table 3. Tobacco smoking and total cancer risk, cohort studies in Japanese population

Reference	Study period	Study population				Category	No. among cases	Relative risk (95 % CI or *P*)	*P* for trend	Confounding variables considered	Comments
		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths						
Kono et al. (1985) (5)	1965–1977	5446 men	Male Japanese physicians	Death	235 deaths	Never	40	1.00		Age	Follow-up by permanent address (Honseki)
		27–89 years old				Past	42	0.95 (0.62–1.47)			
		Mean 49 years old				Current	153	1.60 (1.12–2.30)			
						⩽9 cigarettes/day	19	1.09 (0.63–1.88)			
						10–19	64	1.59 (1.05–2.39)			
						⩾20	64	2.08 (1.37–3.17)	$P < 0.05$		
Kono et al. (1987) (6)	1965–1983	5130 men	Male Japanese physicians	Death	380 deaths	Never/past		1.00		Age, alcohol drinking	Follow-up by permanent address (Honseki)
		27–89 years old				1–19 cigarettes/day		1.38 (1.07–1.77)			
		Mean 49 years old				⩾20		1.54 (1.15–2.05)			
Hirayama 1990 (7)	1965–1982	122 261 men	95% census population	Death	8794 men	Non-smoker		1.00		Age	Follow-up by death certificates, residential registry, 90% CI
		142 857 women				Daily smoker		1.65 (1.56–1.76)			
		⩾40 years old				⩽59 years old		1.40			
						60–69 years old		1.64			
						⩾70 years old		1.77			
						Non-smoker		1.00			
						1–9 cigarettes/day		1.42 (1.31–1.54)			
						10–19		1.58 (1.49–1.67)			
						⩾20		1.86 (1.75–1.97)			
						Non-smoker		1.00			
						Start ⩽19 years old		1.76 (1.63–1.89)			
						⩾20		1.61 (1.53–1.70)			
						Non-smoker		1.00			
						1–4 years after cessation		1.49 (1.27–1.74)			
						5–9		1.45 (1.19–1.78)			
						⩾10		0.95 (0.76–1.19)			
					5946 women	Never		1.00			
						Daily smoker		1.32 (1.24–1.41)			
						Non-smoker		1.00			
						1–9 cigarettes/day		1.31 (1.20–1.44)			
						10–19		1.33 (1.20–1.47)			
						⩾20		1.44 (1.18–1.78)			
						Non-smoker		1.00			

						Start ⩽19 years old		1.24 (0.86–1.78)			
						⩾20		1.30 (1.21–1.40)			
						Non-smoker		1.00			
						1–4 years after cessation		1.58 (1.02–2.43)			
						5–9		1.21 (0.61–2.39)			
						⩾10		1.22 (0.62–2.41)			
Akiba et al. (1994) (8)	1963–1987	93 000 atomic bomb survivors, 27 000 non-exposed subjects	RERF LLS life Span Study Cohort (atomic bomb survivors and non-exposed subjects)	Incidence	2817 men and 2435 women	First survey				Age, sex, address, year of birth, year of start, socio-economic status, exposure to atomic bomb	Follow-up by RERF cancer registry and death certificates
						Never		1.00			
						Ex-smoker		1.1 (1.0–1.3)			
						Current smoker		1.5 (1.4–1.7)			
						All surveys					
						Never		1.00			
						Ex-smoker		1.2 (1.1–1.4)			
						Current smoker		1.6 (1.5–1.7)			
Takezaki et al. (1999) (9)	1988–1997	3541 men (40–79 years old)	Residential register (response rate 80%)	Death	153 men	Never/quit 1+ year	55	0.59 (0.42–0.83)		Age	Follow-up by residential register and death certificate
						Quit <1 year	5	1.15 (0.48–2.91)			
						Current	92	1.00			
		4121 women			87 women	Never/quit 1+ year	77	0.61 (0.27–1.41)			
						Quit <1 year	1	3.10 (0.37–25.77)			
						Current	6	1.00			
Hara et al. (2002) (10)	1990–1999	19 950 men	Residential registry	Death	424 men	Never	75	1.00		Age, area, education, medication, hypertension, leisure-time physical exercise, vegetable, fruit, fish, pickles, soy and red meat intake, alcohol, BMI	Follow-up by residential register and death certificate
						Past	82	1.09 (0.77–1.54)			
						Current	267	1.61 (1.20–2.15)			
						⩽19 Pack-year	46	1.33 (0.88–2.00)			
						20–29	53	1.41 (0.94–2.10)			
						⩾30	168	1.83 (1.34–2.51)	$P < 0.01$		
						1–19 cigarettes/day	78	1.00			
						20–29	135	1.21 (0.89–1.64)			
						⩾30	54	1.00 (0.68–1.47)	$P = 0.80$		
						Start ⩽19 years old	65	1.00			
						20–24	164	0.86 (0.63–1.17)			
						⩾25	38	0.77 (0.49–1.19)	$P = 0.21$		
		21 534 women			246 women	Never	219	1.00			
						Past	3	0.89 (0.28–2.81)			
						Current	24	1.83 (1.14–2.95)			
						⩽9 Pack-year	7	1.03 (0.42–2.52)			
						10–19	2	0.64 (0.16–2.61)			

Table 3. *Continued*

Reference	Study period	Study population				Category	No. among cases	Relative risk (95 % CI or *P*)	*P* for trend	Confounding variables considered	Comments
		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths						
						⩾20	15	4.51 (2.45–8.30)	$P < 0.01$		
						1–19 cigarettes/day	11	1.00			
						20–29	9	1.77 (0.60–5.17)			
						⩾30	4	6.03 (1.36–26.64)	$P = 0.01$		
						Start ⩽24 years old	8	1.00			
						⩾25	16	0.63 (0.20–1.92)	$P = 0.22$		
Kawaminami et al. (2003) (11)	1980–1999	9629 subjects (30+ years old) NIPPON DATA80	National cardiovascular survey (random sampling)	Death	345 men	Never	48	1.00		Age, body mass index, place of residence, alcohol drinking habit	Follow-up by residential register and death certificate
						Past	67	1.17 (0.80–1.70)			
						Current	230	1.62			
						⩽20 cigarettes/day	150	1.39 (0.99–1.93)			
						21–40	70	1.77 (1.21–2.58)			
						⩾41	10	1.70 (0.85–3.40)			
					233 women	Never	205	1.00			
						Past	5	0.79 (0.32–1.94)			
						Current	23	1.09			
						⩽20 cigarettes/day	22	1.15 (0.73–1.81)			
						21–40	1	0.75 (0.10–5.45)			
						⩾41	0				
Inoue et al. (2004) (12)	1990–2001	44 521 men	Residential registry (40–69 years old)	Incidence	2969 men	Never	488	1.00		Age, area, alcohol, BMI, green vegetable intake	Follow-up by residential register and death certificate
						Past	777	1.37 (1.22–1.54)			
						Current	1704	1.64 (1.48–1.82)			
						⩽19 Pack-year	190	1.26 (1.06–1.49)			
						20–29	307	1.54 (1.33–1.79)			
						30–39	168	1.76 (1.54–2.08)			
						⩾40	168	1.76 (1.56–1.98)	$P < 0.001$		
						1–19 cigarettes/day	483	1.48 (1.29–1.68)			
						20–29	796	1.71 (1.52–1.93)			
						⩾30	425	1.72 (1.51–1.98)	$P < 0.05$		
						Start 25+ years old	65	1.50 (1.28–1.74)			
						20–24	164	1.62 (1.45–1.82)			
						⩽19	38	1.81 (1.58–2.08)	$P < 0.05$		
				Death	1411 men	Never	223	1.00			
						Past	351	1.35 (1.13–1.78)			
						Current	837	1.78 (1.53–2.09)			
						⩽19 Pack-year	96	1.49 (1.16–1.91)			

			20–29	153	1.75 (1.41–2.17)	
			30–39	220	1.86 (1.53–2.26)	
			⩾40	367	1.76 (1.56–2.22)	NS
			1–19 cigarettes/day	244	1.64 (1.35–198)	
			20–29	391	1.86 (1.56–2.21)	
			⩾30	202	1.84 (1.51–2.25)	NS
			Start 25+ years old	142	1.65 (1.32–2.06)	
			20–24	473	1.71 (1.45–2.03)	
			⩽19	222	2.11 (1.73–2.57)	$P < 0.05$
48 271 women	Incidence	1953 women	Never	1779	1.00	
			Past	37	1.47 (1.05–2.05)	
			Current	137	1.46 (1.21–1.75)	
			⩽19 Pack-year	80	1.34 (1.06–1.69)	
			20–29	30	1.78 (1.20–2.63)	
			30–39	10	1.32 (0.71–2.47)	
			⩾40	17	1.83 (1.13–2.96)	NS
			1–19 cigarettes/day	90	1.45 (1.16–1.81)	
			20–29	32	1.42 (0.99–2.03)	
			⩾30	15	1.63 (0.98–2.72)	NS
			Start 25+ years old	92	1.39 (1.12–1.73)	
			20–24	40	1.73 (1.24–2.41)	
			⩽19	5	1.10 (0.45–2.66)	NS
	Death	721 women	Never	656	1.00	
			Past	10	1.03 (0.53–1.99)	
			Current	55	1.58 (1.18–2.12)	
			⩽19 Pack-year	23	1.08 (1.69–1.67)	
			20–29	20	3.37 (2.09–5.44)	
			30–39	7	2.18 (1.03–4.62)	
			⩾40	8	1.26 (0.52–3.06)	NS
			1–19 cigarettes/day	32	1.36 (0.93–2.00)	
			20–29	16	1.99 (1.20–3.31)	
			⩾30	7	1.96 (0.93–4.15)	NS
			Start 25+ years old	35	1.41 (0.99–2.00)	
			20–24	18	2.22 (1.34–3.70)	
			⩽19	2	1.36 (0.34–5.51)	NS

MAIN FEATURES AND COMMENTS

A total of eight cohort studies were identified (Table 3). Among them, four presented results by gender (7,9,11,12), one for men only (5), and one for men and women combined only (8). No case–control studies of the association between tobacco smoking and total cancer risk were identified.

After excluding two studies due to the unavailability of a point estimate or CIs (6,9) and one due to a shorter study analysis period than another study of the same population (10), four results for men, three for women and one for men and women combined were available for further evaluation. A summary of the magnitude of association for these studies is shown in Table 4. In men, all studies consistently showed a moderately increased risk (↑↑) of total cancer in current smokers compared with never-smokers. The study with men and women combined also showed moderately increased risk. The increase in risk in women was weaker than that in men,

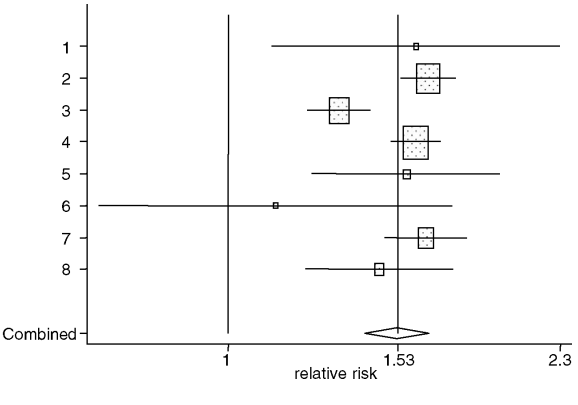
Table 4. Summary of the association between tobacco smoking and total cancer risk

Reference	Study period	Study population						Strength of association
		Sex	No. of subjects	Age range	Event	No. of incident cases or deaths	Relative risk for current smokers vs never-smokers	
Kono et al. (1985 (5)	1965–1977	Men	5130	27–89	Death	380	1.60 (1.12–2.30)	↑↑
Hirayama (1990) (7)	1965–1982	Men	122 261	⩾40	Death	8794	1.65 (1.56–1.76)	↑↑
		Women	142 857	⩾40	Death	5946	1.32 (1.24–1.41)	↑
Akiba et al. (1994) (8)	1963–1987	Men and women	≈120 000	Not specified	Incidence	5252	1.6 (1.5–1.7)	↑↑
Kawaminami et al. (2003) (11)	1980–1999	Men	9629*	⩾30	Death	345	1.56 (1.23–1.98)**	↑↑
		Women			Death	233	1.13 (0.72–1.75)**	–
Inoue et al. (2004) (12)	1990–2001	Men	44 521	40–69	Incidence	2969	1.64 (1.48–1.82)	↑↑
		Women	48 271	40–69	Incidence	1411	1.46 (1.21–1.75)	↑

*Data available only for men and women combined.
**RR and 95% CI estimated by meta-analysis of respective estimates for daily amount of smoking by category. References (6) and (9) were excluded from the meta-analysis since point estimate or confidence intervals were not available or could not be estimated from other given values.
Reference (10) was excluded from the meta-analysis due to its shorter study period than in other reports from the same population.

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

Study No.	Author	Reference	Year	Sex	Design	Event	Current smokers RR	(95% CI)
1	Kono	5	1985	M	CH	Death	1.60	(1.12–2.30)
2	Hirayama	7	1990	M	CH	Death	1.65	(1.54–1.77)*
3	Hirayama	7	1990	F	CH	Death	1.32	(1.22–1.43)*
4	Akiba	8	1994	MF	CH	Incidence	1.60	(1.50–1.70)
5	Kawaminami	11	2003	M	CH	Death	1.56	(1.23–1.98)**
6	Kawaminami	11	2003	F	CH	Death	1.13	(0.72–1.75)**
7	Inoue	12	2004	M	CH	Incidence	1.64	(1.48–1.82)
8	Inoue	12	2004	F	CH	Incidence	1.46	(1.21–1.75)
	Summary estimates (random effect model)					Total	1.53	(1.41–1.65)
	(Test for heterogeneity: Q = 23.364 with df = 7, P = 0.001)							
						Men	1.64	(1.55–1.73)
						Women	1.34	(1.24–1.43)



RR, relative risk; CH, cohort study; NA, not available, M, male; F, female.
The boxed area represents the contribution of each study (weight) to the meta-analysis.
*95% CI of reference (7) estimated from the given RR and 90% CI.
**RR and 95% CI of reference (11) estimated by meta-analysis of the respective estimates for daily amount of smoking by category.
References (6) and (9) were excluded from the meta-analysis since point estimate or confidence intervals were not available or could not be estimated from other given values.
Reference (10) was excluded from the meta-analysis due to its shorter study period than in other reports from the same population.

with two studies showing a weakly increased risk (↑) and one showing no association (–).

The summary relative risk was estimated by meta-analysis using a random effect model (test for heterogeneity: Q = 23.364 with df = 7, $P = 0.001$) as 1.53 (95% CI 1.41–1.65) for men and women combined, 1.64 (95% CI 1.55–1.73) for men and 1.34 (95% CI 1.24–1.43) for women (Fig. 1).

In the IARC evaluation (1), no evaluation was made on tobacco smoking and total cancer risk. However, the study concluded that tobacco smoking and tobacco smoke are carcinogenic to humans, and that there was sufficient evidence of a causal relationship in humans with most sites of cancer. We therefore assumed that the association between tobacco smoking and total cancer risk holds biological plausibility.

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

From these results and assumed biological plausibility, we conclude that there is convincing evidence that current tobacco smoking moderately increases the risk of total cancer in the Japanese population compared with never-smoking Japanese (∼1.5 times, or 1.6 in men and 1.3 in women).

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