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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,

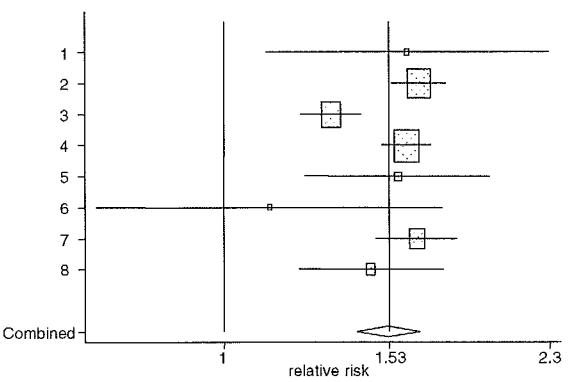
Table 4. Summary of the association between tobacco smoking and total cancer risk

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

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Background: It is unclear whether tobacco smoking is related to colorectal cancer risk in Japan. We evaluated the association among the Japanese population based on a systematic review of epidemiologic evidence.

Methods: Original data were obtained from searches of MEDLINE using PubMed, complemented with manual searches. The 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.

Results: A total of six cohort studies and 15 case–control studies were thus identified. A substantial degree of heterogeneity was observed in the association between smoking and colon cancer; most case–control studies published before 1994 reported an inverse association, whereas studies conducted over the last decade did not find any significant association. Recent cohort studies have shown a non-significant 20–40% increase in colon cancer risk associated with current smoking. Several recent case–control studies and some cohort studies have identified a weak to strong positive association between smoking and rectal cancer.

Conclusion: We conclude that tobacco smoking possibly increases the risk of colorectal cancer among the Japanese population. More specifically, tobacco smoking may possibly increase the risk of rectal cancer; however, epidemiologic evidence is still insufficient to demonstrate any clear association with colon cancer.

INTRODUCTION

In Japan, colorectal cancer has markedly increased over the last several decades (1) and it is now among the highest levels in the world (2). The increase in mortality has been linked to dietary changes including a decreased consumption dietary fibers (3) or grains (4). However, the increasing male-to-female mortality ratio from colorectal cancer since 1970 in Japan (1) may have been a result of sex differences in health-related lifestyles including tobacco smoking.

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Tobacco smoke contains numerous chemicals that are potentially carcinogenic to humans. The range of cancer sites associated with tobacco smoking has been expanded and the International Agency for Research on Cancer (IARC) (5) recently admitted cancers of several sites including stomach and liver as smoke-related. Although colorectal cancer has not formally been recognized as a smoke-related cancer, a review identified emerging evidence showing an increased risk of colorectal cancer associated with smoking, especially long-term smoking (6). However, such an association has been reported mainly from the United States, whereas the findings from other populations remain conflicting.

The objective of the present study was to review the epidemiological findings regarding the association between smoking and colorectal cancer among Japanese population.

The study results were summarized and the magnitude of the association was assessed. This work was conducted as part of a project of systematic evaluation of the epidemiological evidence regarding lifestyles and cancers in Japanese (7).

METHODS

The 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 epidemiologic studies on the association between tobacco smoking and colorectal cancer incidence or mortality among Japanese from 1963 to 2004, including papers in press if available, were identified using the search terms 'tobacco smoking', 'colorectal cancer', 'colon cancer', 'rectal cancer', 'cohort studies', 'case–control studies', 'Japan' and 'Japanese' as keywords found in the abstract. Papers written in either English or Japanese were reviewed, and only studies on Japanese population living in Japan were included. The individual results were summarized in the tables separately by a study design as cohort or case–control studies and, if available, by cancer site as colon, rectum or colorectum.

An evaluation was made based on the magnitude of association and the strength of evidence. First, the relative risks in each epidemiologic study were grouped by the magnitude of association, while considering 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 to 2 (SS) or (iii) 0.5 to <0.67 (SS); weak, 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, 0.67 to 1.5 (NS). In the case of multiple publications of analyses of the same or overlapping datasets, only data from the largest or most updated results were included, and the incidence was given priority over mortality as an outcome measure. The incidence was also given priority in a single publication describing both incidence and mortality. After this process, the strength of evidence was evaluated in a similar manner to that used in the WHO/FAO Expert Consultation Report (8), in which evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. We assumed that biological plausibility corresponded to the judgment of the most recent evaluation from IARC (5). Notwithstanding the use of this quantitative assessment rule, an arbitrary assessment cannot be avoided when considerable variation exists in the magnitude of association between the results of each study. The final judgment, therefore, was made based on a consensus of the research group members, and it was therefore not necessarily objective. When we reach a conclusion that there is 'convincing' or 'probable' evidence of an association, we conduct a meta-analysis to obtain summary estimates for the overall magnitude of association.

MAIN FEATURES AND COMMENTS

A total of six cohort studies and 15 case–controls studies were identified (Table 1 and Table 2, respectively). Among the cohort studies, four presented results by gender (10,12–14), one for men only (9), and one only for men and women combined (11). The respective numbers for the case–control studies are three, four and eight. Two case–control studies that did not indicate a point estimate and confidence interval, or *P*-value, were excluded (15,27), and a summary of the magnitude of association for the remaining studies is shown in Tables 3 and 4 for the cohort studies and case–control studies, respectively.

Among the five cohort studies showing relative risks separately for the colon and rectum, no study found a significant association with colon cancer, although recent cohort studies (12–14) reported a non-significant 20–40% increased risk for colon cancer associated with smoking. For rectal cancer, one study (10) found a weak positive association in both men and women, whereas another study (12) reported a strong positive association in men. Of the two cohort studies showing relative risk for colon and rectum combined, a nation-wide study (13) reported a weak positive association in men. This study also found marginally significant associations in a separate analysis for the colon and rectum; the respective relative risks (95% confidence intervals) of current smoking compared with never-smoking were 1.4 (0.99–1.9) and 1.4 (0.9–2.3).

Of the 13 case–control studies evaluated, 11 studies provided odds ratios for the colon and rectum separately. Among these studies, five (17–20,22) of six studies published before 1994 have identified a reduced risk of colon cancer associated with smoking, whereas no study published after 1994 showed either a positive or inverse association with colon cancer. For rectal cancer, of five relevant studies published after 1994, four (23–25,29) have shown a weak or moderate positive association and the remaining study (28) reported a significant trend association with smoking index (P for trend = 0.04), whereas studies published before 1994 did not find any significant association. Of the four case–control studies reporting odds ratio for the colon and rectum combined (16,21,26,28), one study (26) found a significantly increased risk associated with smoking, especially with smoking in the distant past.

Four cohort studies (9,12–14) and two case–control studies (26,29) adjusted for alcohol consumption, but few studies controlled for other dietary (14) and non-dietary factors including sports activities (13,14) and obesity (12–14,26). Three case-control studies were performed on a community basis for recruiting control subjects (20–22), whereas the remaining studies were conducted using either hospital-based, health center-based or screening-based design.

Numerous studies including Japanese one (30) have identified smoking as a risk factor for colorectal adenomas, a precursor of colorectal cancer. Among the Japanese studies reviewed; however, we found a substantial heterogeneity in the risk estimates for an association between smoking and colon cancer, including marginally significant positive association in a nation-wide cohort study (13) and an inverse association in several case–control studies (17–20,22). Interestingly, all case–controls studies that reported an inverse association with colon cancer were published before 1994.

Table 1. Tobacco smoking and colorectal cancer risk, cohort study in Japanese population

References	Study period	Study population				Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths					
Kono et al. 1987 (9)	1965–83	5130 men	Male physicians	Death	Large bowel	Never/past		1.00		Age and alcohol drinking
					39	Current		NA		
						Up to 19 cigs/day		0.89 (0.42–1.87)		
						20+		0.93 (0.39–2.21)		
Akiba and Hirayama 1990 (10)	1965–82	265 118 (122 261 men, 142 857 women)	Six prefecture cohort of census population	Death	Colon	Never	43	1.0	>0.1	Age, residence and occupation
					190 men	Current	147	1.1 (0.8–1.5)		
						1–4 cigs/day	3	0.9 (0.2–2.6)		
						5–14	62	1.0 (0.7–1.6)		
						15–24	69	1.2 (0.5–2.4)		
						25–34	8	1.8 (0.6–4.2)		
						35+	5	1.1 (0.8–1.5)		
					Colon	Never	232	1.0	>0.1	
					257 women	Current	25	0.9 (0.6–1.3)		
						1–4 cigs/day	5	1.1 (0.4–2.4)		
						5–14	18	0.9 (0.5–1.4)		
						15+	2	0.5 (0.1–1.6)		
					Rectum	Never	50	1.0	0.09	
					254 men	Current	204	1.4 (1.0–1.9)		
						1–4 cigs/day	5	1.4 (0.5–3.2)		
						5–14	85	1.3 (0.9–1.9)		
						15–24	101	1.4 (1.0–2.0)		
						25–34	10	1.5 (0.7–2.9)		
						35+	3	1.1 (0.3–2.9)		
					Rectum	Never	189	1.0	>0.1	
					211 women	Current	22	0.9 (0.6–1.5)		
						1–4 cigs/day	2	0.5 (0.1–1.7)		
						5–14	14	0.9 (0.5–1.5)		
						15+	6	2.1 (0.8–4.3)		
Akiba 1994 (11)	1963–87	61 505 men and women	RERF Life Span Study (atomic bomb survivors and non-exposed subjects)	Incidence	Colon	Never		1.0		City, sex, population group, atomic bomb exposure, year of birth and age
					324 (M: 172; F: 152)	Past		0.9 (0.6–1.4)		
						Current		1.2 (0.9–1.6)		
					Rectum	Never		1.0		

Table 1. *Continued*

References	Study period	Study population				Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths					
					218 (M: 122; F: 96)	Past		1.3 (0.8–2.0)		
						Current		1.0 (0.7–1.4)		
Shimizu et al. 2003 (12)	1993–2000	29 051 (13 392 men, 15 659 women)	Residents in Takayama city	Incidence	Colon 104 men	Never	16	1.00	0.19	Age, body height, body mass index, alcohol intake and year of education
						Current				
						Up to 20 pack-years	41	1.36 (0.79–2.33)		
						>20	47	1.37 (0.81–2.32)		
					Colon	Never	68	1.00	0.54	
					77 women	Current				
						Up to 10 pack-years	4	0.59 (0.21–1.62)		
						>10	5	0.77 (0.30–1.96)		
					Rectum	Never	7	1.00	0.04	
					57 men	Current				
						Up to 20 pack-years	16	1.33 (0.57–3.12)		
						>20	34	2.44 (1.12–5.30)		
					Rectum	Never	32	1.00	0.63	
					38 women	Current				
						Up to 10 pack-years	4	1.76 (0.60–5.14)		
						>10	2	0.94 (0.21–4.16)		
Otani et al. 2003 (13)	1990–99	90 004 (42 540 men, 47 464 women)	JPHC study (cohort I: 5 prefectures, cohort II: 6 prefectures), residential registry	Incidence	Colorectum	Never	78	1.00		Age, family history of colorectal cancer, body mass index, alcohol consumption, physical exercise and area
					447 men	Past	124	1.3 (0.98–1.7)		
						Current	245	1.4 (1.1–1.8)	0.47 among current smokers	
						Up to 20 pack-years	33	1.1 (0.8–1.7)		
						20–29	50	1.3 (0.9–1.9)		
						30–39	73	1.4 (1.05–2.0)		
						40+	83	1.4 (0.99–1.8)		
					Colon	Never	53	1.00		
					298 men	Past	86	1.4 (0.96–1.9)		

						Current	160	1.4 (0.99–1.9)	0.16 among current smokers	
						Up to 20 pack-years	17	0.9 (0.5–1.5)		
						20–29	31	1.2 (0.8–2.0)		
						30–39	55	1.7 (1.1–2.4)		
						40+	54	1.3 (0.9–2.0)		
					Rectum	Never	25	1.0		
					148 men	Past	38	1.2 (0.7–2.0)		
						Current	85	1.4 (0.9–2.3)	0.48 among current smokers	
						Up to 20 pack-years	16	1.6 (0.9–3.0)		
						20–29	19	1.5 (0.8–2.7)		
						30–39	18	1.0 (0.6–1.9)		
						40+	29	1.4 (0.8–2.3)		
					Colorectum	Never	239	1.0		
					259 women	Past	4	1.3 (0.5–3.6)		
						Current	16	1.4 (0.8–2.4)		
Wakai et al. 2003 (14)	1988–97	59 879 (25 260 men, 34 619 women)	JACC study (24 areas throughout Japan)	Incidence	Colon	Never	39	1.00		Area, age, education, family history of colorectal cancer in parents or siblings, body mass index, alcohol drinking, walking time, sedentary work, consumption of green leafy vegetables and beef
					219 men	Past	67	1.07 (0.72–1.59)		
						Current	113	1.23 (0.85–1.78)		
					Colon	Never	175	1.00		
					189 women	Past	4	1.07 (0.39–2.92)		
						Current	10	1.06 (0.55–2.02)		
					Rectum	Never	34	1.00		
					147 men	Past	44	0.88 (0.56–1.39)		
						Current	69	0.83 (0.55–1.26)		
					Rectum	Never	55	1.00		
					57 women	Past	1	1.05 (0.14–7.69)		
						Current	1	0.36 (0.05–2.65)		

Table 2. Tobacco smoking and colorectal cancer risk, case–control study in Japanese population

References	Study time	Study subjects				Category	Odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
Kondo 1975 (15)	1967–73	Hospital-based (three hospitals in Nagoya)	Case: 91% were histologically confirmed: Control: inpatients without history of cancer of the digestive organs, oral cavity, pharynx, lung, or larynx, or other diseases of the colorectum	Colon					Matched (1 : 2) for age (±5 years) and sex	*Total number of controls for colorectal cancer cases. Number for each site was not shown. Odds ratio was calculated based on numbers of cases and controls presented in table
				93 men	406 men*	Non-smoker	1.00			
						Current	0.50			
						1–20 cigs/day	0.66			
						21+	0.22			
				86 women	174 women*	Non-smoker	1.00			
						Smoker	0.52			
						1–10 cigs/day	0.69			
						11+	0.23			
				Rectum						
				112 men	406 men*	Non-smoker	1.00			
						Current	0.95			
						1–20 cigs/day	1.11			
						21+	0.71			
				99 women	174 women*	Non-smoker	1.00			
						Smoker	0.70			
						1–10 cigs/day	1.10			
						11+	0.21			
Haenszel et al. 1980 (16)	(not described)	Hospital-based (Hiroshima, Aichi, Miyagi)	Case: 89% were histologically confirmed; Control: inpatients without gastric and duodenal ulcers, other disease of the large bowel, or other cancers of the digestive system	284 men and women	571 men and women	Never smoking	1.00		Matched (1 : 2) for age, sex and hospital (prefecture)	
						Any smoking	0.77 (n.s.)			
Watanabe et al. 1984 (17)	1977–83	Hospital-based (five hospitals in Kyoto, Shiga, Hyogo)	Case: histologically confirmed cases; Control: inpatients without history of cancer or any diseases of large bowel	Colon					Matched (1 : 1) for hospital, sex and age (±5 years)	
				138 men and women	138 men and women	Non-smoker	1.00			
						Smoker	0.26 (0.13–0.53)			

						1–20 cigs/day	0.53 (0.31–0.89)		
						21+	0.46 (0.21–1.03)		
				Rectum					
				65 men and women	65 men and women	Non-smoker	1.00		
						Smoker	0.71 (0.34–1.47)		
Tajima and Tominaga 1985 (18)	1981–83	Hospital-based (Aichi Cancer Center)	Case: histologically confirmed cases; Control: inpatients without history of cancer	Colon				Adjusted for age	*Common controls for cases of cancer of the stomach, colon or rectum
				27 men	111 men*	Never	1.00		
						Current	0.61 (n.s.)		
					Brinkman index	Never	1.00		
						<600 cig-years	0.33 (n.s.)		
						600+	0.82 (n.s.)		
					Starting age	Never	1.00		
						20+ years old	0.71 (n.s.)		
						Up to 19	0.15 (n.s.)		
				Rectum					
				25 men	111 men*	Never	1.00		
						Current	1.02 (n.s.)		
					Brinkman index	Never	1.00		
						<600 cig-years	1.06 (n.s.)		
						600+	0.93 (n.s.)		
					Starting age	Never	1.00		
						20+ years old	1.18 (n.s.)		
						Up to 19	0.78 (n.s.)		
Kato et al. 1990 (19)	1979–87	Registry-based (Aichi Cancer Registry)	Case: histologically confirmed (90%); Control: cases with smoking-unrelated cancers	Colon				Adjusted for age	*Patients with smoking-related cancers were excluded
				1716 men	16600 men*	Non-smoker	1.00		
						Smoker	0.78 (0.70–0.88)		
				Proximal colon (n = 445)		Non-smoker	1.00		
						Smoker	0.70 (0.57–0.87)		
				Distal colon (n = 765)		Non-smoker	1.00		
						Smoker	0.83 (0.71–0.98)		
				Rectum					
				1611 men	16600 men*	Non-smoker	1.00		
						Smoker	0.93 (0.82–1.05)		

Table 2. *Continued*

References	Study time	Study subjects				Category	Odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
Kato et al. 1990 (20)	1986–90	Population-based (Aichi)	Case: histologically confirmed cases at Aichi Cancer Center Hospital: Control: population controls randomly selected through telephone directories	Colon					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)*	Never	1.00			
						Past	1.12 (0.60–2.10)			
						Current	0.59 (0.32–1.11)			
				Rectum						
				91 (M: 60; F: 31)	578 (M: 377; F: 201)*	Never	1.00			
						Past	1.54 (0.70–3.42)			
						Current	1.44 (0.69–2.99)			
Yoshida et al. 1992 (21)	1987–90	Population-based (Sapporo)	Case: patients diagnosed at the First Department of Surgery of Sapporo Medical University or its affiliated hospitals; Control: selected from telephone books	Colon					Matched (1 : 2) for sex, sex, age (±3 years) and registered residence	
				177 (M: 81; F: 96)	354 (M: 162; F: 192)	Never, past, sometimes	1.00			
						Current (everyday)	0.79 (0.51–1.22)			
				Rectum						
				153 (M: 90; F: 63)	306 (M: 180; F: 126)	Never, past, sometimes	1.00			
						Current (everyday)	0.89 (0.55–1.45)			
Hoshiyama et al. 1993 (22)	1984–90	Population-based (Saitama)	Case: histologically confirmed cases at the Saitama Cancer Center Hospital; Control: population controls taken from seven provincial cities and two towns in the vicinity of the hospital	Colon					Adjusted for sex and age	*Common controls for cases of cancer of the colon and rectum
				79 (M: 37; F: 42)	653 (M: 343; F: 310)*	Never	1.0			
						Past	0.3 (0.1–0.8)			
						Current				
						1–29 cigs/day	0.3 (0.1–0.7)			
						30+	0.3 (0.1–1.0)			
					Cigarette years	Never (0)	1.0	<0.01		
						Up to 800 cig-years	0.3 (0.1–0.7)			
						>800	0.2 (0.0–0.7)			

				Rectum						
				102 (M: 61; F: 41)	653 (M: 343; F: 310)*	Never	1.0			
						Past	1.4 (0.6–3.1)			
						Current				
						1–29 cigs/day	1.7 (0.9–3.1)			
						30+	1.0 (0.3–2.6)			
					Cigarette years	Never (0)	1.0	0.31		
						Up to 800 cig-years	1.6 (0.8–3.0)			
						>800	1.5 (0.6–3.6)			
Kotake et al. 1995 (23)	1992–94	Hospital-based (10 hospitals in Kanto region)	Case: histologically confirmed cases; Control: screening controls and hospital controls, including cancer patients	Colon						
				187 (M: 111; F: 76)	187 (M: 111; F: 76)	Never	1.0		Matched for sex and age (5 year age group)	
						Past	–			
						Current	1.3 (0.3–5.2)			
					Cigarette years	Never (0)	1.0			
						Up to 400 cig-years	–			
						>400	0.8 (0.2–2.8)			
				Rectum						
				176 (M: 103; F: 73)	176 (M: 103; F: 73)	Never	1.0			
						Past	–			
						Current	1.4 (0.3–6.8)			
					Cigarette years	Never (0)	1.0			
						Up to 400 cig-years	–			
						>400	2.7 (0.9–8.3)			
Inoue et al. 1995 (24)	1988–92	Hospital-based (Aichi Cancer Center Hospital)	Case: histologically confirmed cases; Control: first-visit outpatients free from cancer	Colon: proximal					Adjusted for age	*Common controls for cases of cancer of the colon and rectum
				51 men	8621 men*	Never	1.0			
						Ever (habitual)	0.7 (0.5–1.4)			
				43 women	23 161 women*	Never	1.0			
						Ever (habitual)	0.9 (0.4–2.4)			
				Colon: distal						
				75 men	8621 men*	Never	1.0			
						Ever (habitual)	1.0 (0.6–1.7)			
				62 women	23 161 women*	Never	1.0			
						Ever (habitual)	1.1 (0.6–2.3)			

Table 2. *Continued*

References	Study time	Study subjects				Category	Odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
				Rectum						
				131 men	8621 men*	Never	1.0			
						Ever (habitual)	1.9 (1.1–3.2)			
				70 women	23 161 women*	Never	1.0			
						Ever (habitual)	1.7 (1.0–3.1)			
Murata et al. 1996 (25)	1984–93	Screening-based (participants of stomach cancer screening)	Case: confirmed by a record linkage to cancer registry data; Control: screenees free from any cancer during the follow-up period	Colon						
				61 men	122 men	Non-smoker*	1.0	n.s.	Matched (1 : 2) for sex, birth year (±2 years) and residence	*Non-smoker, including lifetime never-smoker and past smoker (who had quit for 2 years or more); smoker, including those who had quit smoking within the past 2 years
						Smoker*				
						1–10 cigs/day	0.8 (n.s.)			
						11–20	1.1 (n.s.)			
						21+	1.0 (n.s.)			
				Rectum						
				43 men	86 men	Non-smoker	1.0	n.s.		
						Smoker				
						1–10 cigs/day	1.3 (n.s.)			
						11–20	1.1 (n.s.)			
						21+	3.0 (n.s.)			
Yamada et al. 1997 (26)	1991–93	Health check-up based (PL Tokyo Health Care Center: multiphasic health check-up program)	Case: histologically confirmed cases; Control: examinees without history of colorectal cancer and inflammatory bowel disease	Colorectum						
				66 (M: 55; F: 11)	132 (M: 110; F: 22)	Never	1.0	0.8	Matched (1 : 2) for sex, age and history of previous health check-up at the Center; Adjusted for body mass index and alcohol consumption	Results for carcinoma *in situ* ($n = 129$) were also presented

						Past	1.8 (0.7–4.4)			
						Current				
						1–15 cigs/day	1.2 (0.4–3.8)			
						16–30	0.8 (0.3–2.1)			
						31+	2.4 (0.7–8.6)			
						Pack-years				
						0 pack-year	1.0	0.02		
						1–20	0.8 (0.3–2.2)			
						21–40	1.2 (0.5–3.0)			
						41+	2.6 (0.9–7.1)			
						Within the past 20 years				
						0 pack-year	1.0	0.1		
						1–15	1.1 (0.5–2.7)			
						16–30	1.2 (0.5–2.9)			
						31+	2.9 (0.9–9.4)			
						Until 20 years ago				
						0 pack-year	1.0	0.005		
						1–15	1.0 (0.4–2.4)			
						16–30	3.4 (1.2–9.2)			
						31+	5.0 (1.3–18.3)			
Ping et al. 1998 (27)	1986–94	Health check-up based (Tokay University Hospital; source: health check-up examinees at the hospital)	Case: histologically confirmed cases; Control: cancer-free examinees	Colorectum					Matched (1 : 3) for sex, age (±2 years), date of health checking (±3 months) and residence; excluded 35 controls owing to the lack of information on lifestyle	*Odds ratio (not presented in the paper) was calculated according to figures in table. Description of method is unclear
				100 (M: 77; F: 23)	265 men and women	Never	1.0			
						Past	1.4*			
						Current	1.5*			
Murata et al. 1999 (28)	1989–97	Hospital-based case-control study (Chiba Cancer Center Hospital)	Case: those who underwent surgery; Control: outpatients free from cancer	Colorectum						
				267 men	395 men	Non-smoker	1.00	0.1	Adjusted for age (10 year age group)	
						Smoker				
						<20 cigs/day	1.03 (0.64–1.6)			
						20–29	1.20 (0.80–1.8)			
						30+	1.16 (0.73–1.8)			
				Colon						
				157 men	395 men	Non-smoker	1.00	0.32		

Table 2. *Continued*

References	Study time	Study subjects				Category	Odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
						Smoker				
						<20 cigs/day	0.93 (0.54–1.6)			
						20–29	1.09 (0.68–1.8)			
						30+	0.96 (0.55–1.7)			
				Rectum						
				110 men	395 men	Non-smoker	1.00	0.04		
						Smoker				
						<20 cigs/day	1.17 (0.60–2.3)			
						20–29	1.40 (0.77–2.5)			
						30+	1.50 (0.82–2.7)			
Minami et al. 2003 (29)	1997–2001	Hospital-based case-control study (Miyagi Cancer Center Hospital)	Case: clinical, cytological and/or histopathological examination; Control: non-cancer patients	Colon					Adjusted for age, year of survey, alcohol consumption, family history of index cancer in parents and siblings and occupation	
				184 men	1222 men	Never	1.00			
						Past	0.92 (0.59–1.42)			
						Current	0.90 (0.60–1.35)			
				140 women	1222 women	Never	1.00			
						Past	1.13 (0.38–3.38)			
						Current	1.16 (0.60–2.23)			
				Rectum						
				104 men	1222 men	Never	1.00			
						Past	1.44 (0.76–2.73)			
						Current	1.67 (0.93–3.00)			
				60 women	1222 women	Never	1.00			
						Past	2.12 (0.61–7.34)			
						Current	1.79 (0.82–3.93)			