Table 2. *Continued*

Reference	Study period	Study subjects				Category	Odds ratios (95% CI or *P*)	*P* for trend	Confounding variables considered
		Type and source	Definition	Number of cases	Number of controls				
Stellman et al. (24)	1993–98	Hospital-based (8 hospitals in Aichi Prefecture)	Cases: microscopically confirmed; Controls: hospitalized patients without established smoking-related diseases (hospital controls) or randomly selected residents (community controls)	410 men	252 men (HC)	Never	1.0		Frequency matched for: age (±5 years), hospital (HC), date of interview, and residence (CC); Adjusted for age, education, and hospital (HC)
						Past	1.3 (0.6–2.9)		
						Current	3.5 (1.6–7.5)		
(Aichi portion)						1–19 cigarettes/day	1.6 (0.7–3.9)		
						20–29	3.5 (1.5–8.4)		
						30+	6.2 (2.6–15.0)	$P < 0.001$	
				410 men	411 men (CC)	Never	1.0		
						Past	2.2 (1.3–4.0)		
						Current	6.3 (3.7–10.9)		
						1–19 cigarettes/day	2.6 (1.4–4.9)		
						20–29	4.3 (2.4–7.6)		
						30+	9.3 (5.2–16.7)	$P < 0.001$	
				Male cases of AD	252 men (HC)	Never	1.0		
						Current 1–19 cigarettes/day	0.6 (0.2–1.8)		
						20–29	2.2 (0.8–5.9)		
						30+	3.3 (1.2–8.8)		
				Male cases of AD	411 men (CC)	Never	1.0		
						Current 1–19 cigarettes/day	1.2 (0.5–2.9)		
						20–29	2.9 (1.4–5.9)		
						30+	5.5 (2.7–11.3)		
				Male cases of SQ	252 men (HC)	Never	1.0		
						Current 1–19 cigarettes/day	7.4 (1.3–42.2)		
						20–29	13.7 (2.5–76.2)		
						30+	31.8 (5.4–185.8)		
				Male cases of SQ	411 men (CC)	Never	1.0		
						Current 1–19 cigarettes/day	10.2 (2.2–46.7)		
						20–29	14.1 (3.2–62.1)		
						30+	35.7 (8.1–156.5)		

Ito et al. (25)	1999–2000	Hospital-based (Aichi Cancer Center)	Cases: adenocarcinoma (prevalent cases); Controls: outpatients without a history of cancer who underwent gastroscopy	138 men and women	241 men and women	Never	1.00		Age and sex
						Past	1.18 (0.59–2.34)		
						Current	1.29 (0.67–2.49)		
Minami and Tateno (26)	1997–2001	Hospital-based (Miyagi Cancer Center)	Cases: including cases not microscopically confirmed; Controls: hospitalized non-cancer patients without smoking-related diseases	354 men	1222 men	Never	1.00		Age, year of survey, alcohol consumption, family history of lung cancer, and occupation
						Past	2.74 (1.71–4.38)		
						Current	4.75 (3.04–7.42)		
						Ever	3.82 (2.49–5.86)		
						1–10 cigarettes/day	2.72 ($P < 0.05$)		
						11–20	3.45 ($P < 0.05$)		
						21+	6.09 ($P < 0.05$)	$P = 0.0001$	
				111 male cases of SQ	1222 men	Never	1.00		
						Past	5.72 (2.18–15.0)		
						Current	9.30 (3.59–24.1)		
				53 male cases of SM	1222 men	Never	1.00		
						Past	12.77 (1.67–97.5)		
						Current	21.05 (2.83–156)		
				145 male cases of AD	1222 men	Never	1.00		
						Past	1.47 (0.82–2.63)		
						Current	2.24 (1.31–3.84)		
				161 women	1222 women	Never	1.00		
						Past	2.37 (1.08–5.23)		
						Current	1.91 (1.14–3.18)		
						Ever	2.02 (1.28–3.18)		
						1–10 cigarettes/day	1.45 (NS)		
						11–20	2.35 ($P < 0.05$)		
						21+	0.67 (NS)	$P = 0.047$	
				122 female cases of AD	1222 women	Never	1.00		
						Past	2.57 (1.13–5.85)		
						Current	1.10 (0.57–2.13)		
Marugame et al. (27)	1996–98	Hospital-based (20 hospitals in Osaka, Okinawa, and Nagano)	Cases: microscopically confirmed; Controls: hospitalized patients without smoking-related diseases	839 men	491 men	Never	1.00		Age and prefecture
						Past	2.46 (1.47–4.12)		
						Current	4.56 (3.00–6.94)		
						1–20 cigarettes/day	1.94 (1.31–2.87)		
						21–39	3.38 (2.67–5.05)		

Table 2. *Continued*

Reference	Study period	Study subjects				Category	Odds ratios (95% CI or *P*)	*P* for trend	Confounding variables considered
		Type and source	Definition	Number of cases	Number of controls				
						40+	4.61 (2.80–7.57)		
				288 male cases of SQ	491 men	Never	1.00		
						Past	13.9 (3.16–61.0)		
						Current	24.5 (7.39–80.9)		
				369 male cases of AD	491 men	Never	1.00		
						Past	1.95 (1.09–3.50)		
						Current	2.56 (1.61–4.07)		
				316 women	389 women	Never	1.00		
						Past	0.93 (0.47–1.81)		
						Current	2.29 (1.44–3.64)		
						1–20 cigarettes/day	1.98 (1.18–3.32)		
						21+	4.37 (1.57–12.2)		
				28 female cases of SQ	389 women	Never	1.00		
						Past	9.56 (2.73–33.4)		
						Current	10.9 (3.99–30.0)		
				239 female cases of AD	389 women	Never	1.00		
						Past	0.54 (0.23–1.26)		
						Current	1.48 (0.87–2.51)		

CI, confidence interval; HC, hospital controls, CC, community controls; SQ, squamous cell carcinoma; SM, small cell carcinoma; AD, adenocarcinoma; LA, large cell carcinoma.
NS, not statistically significant.
[a]A possible error in odds ratio or 95% CI (ratio of odds ratio to lower limit of its 95% CI does not equal that of upper limit of 95% CI to odds ratio).

Table 3. Summary table of the association between tobacco smoking and lung cancer risk in cohort studies among Japanese population

Reference	Study period	Study subjects					Magnitude of association[a]
		Sex	Number of subjects	Age (years)	Event	Number of incident cases or deaths	
Kono et al. (9)	1965–83	Men	5130	27–89	Death	74	↑↑↑
Akiba and Hirayama (10)	1966–81	Men	122 261—α	40+	Death	1200	↑↑↑
		Women	142 857—α	40+	Death	394	↑↑↑
Tomita et al. (11)	1975–85	Men	37 645	20–55	Death	32	↑↑
Murata et al. (12)	1984–93	Men	17 200	NA	Incidence	107	↑↑↑
Sobue et al. (1)	1990–99	Men	57 591	40–69	Incidence	324	↑↑↑
		Women	59 103	40–69	Incidence	98	↑↑↑
Pierce et al. (13)	1958–94	Men and women	45 113	NA	Incidence	592	↑↑↑
Ando et al. (3)	1988–97	Men	45 010	40–79	Death	469	↑↑↑
		Women	55 724	40–79	Death	128	↑↑↑
Marugame et al. (2)	1983–2000	Men	44 451	40–79	Death	466	↑↑↑
		Women	43 702	40–79	Death	132	↑↑↑

NA, not available. Akiba and Hirayama (10): 'α'—ex-smokers, occasional smokers, and those for whom age or smoking history information was unavailable were excluded but the number of the excluded subjects was unknown.
[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; –, no association (see Methods for a more detailed definition).

Among the cohort studies, four reported results by gender (1–3,10), three for men only (9,11,12) and one for men and women combined (13). The respective numbers for case–control studies were eight (14–16,21–23,26,27), three (18,20,24) and two (19,25). One study presented results for men only along with those for both genders combined (17).

The magnitude of association for these studies is summarized in Tables 3 and 4 for cohort and case–control studies, respectively. All cohort studies (1–3,9,10,12,13) except one (11) showed a strong positive association (↑↑↑) between current smoking and the risk of lung cancer. The case–control studies (15,17–24,26,27) also consistently reported a similarly strong association except for two investigations in the analysis for women (14,16) and one in the analysis for men and women combined (25). Most of the studies demonstrated clear dose–response relationships between the risk of lung cancer and the number of cigarettes smoked per day (Tables 1 and 2), years of smoking, the pack-year index and/or years since stopped smoking (data not shown in tables). The RRs or odds ratios were generally lower in women than in men, probably due to the female smaller amount of smoking, so that we estimated the summary measure of association by gender (Fig. 1). Therefore, the three studies (13,19,25) that presented findings only for men and women combined were excluded from the meta-analysis.

The summary RR for current smokers versus never smokers was estimated to be 4.39 (95% CI 3.92–4.92) for men and 2.79 (95% CI 2.44–3.20) for women by the meta-analysis using fixed-effect models (test for heterogeneity: $P = 0.17$ for men and $P = 0.14$ for women). We adopted fixed-effect models because the heterogeneity among studies was not statistically significant. Cohort studies and case–control studies gave a reasonably consistent summary measure (Fig. 1). In men, no apparent difference in the RR was found between recent investigations and an earlier cohort study (the follow-up started in 1966) by Akiba and Hirayama (10), while the RR was higher in recent cohort studies (1–3) than in the earlier one (10) in women. To clarify whether women have a smaller risk of lung cancer at the same exposure to tobacco smoking, we attempted to estimate the summary RRs according to the level of exposure by sex. Unfortunately, such summary RRs could not be calculated because only five studies (2,10,14,26,27) reported the RRs or odds ratios by both sex and the amount of cigarette smoking, and they used various cutoffs to categorize subjects according to the consumption level of cigarettes. To address the question, a pooled analysis of original data may be warranted.

The summary RRs comparing current and never smokers derived from the present meta-analysis are much lower than the corresponding RRs in Western countries (1). This discrepancy in the relative risk has been extensively discussed by Sobue et al. (1) and Marugame et al. (2) and may be attributable to both the lower risk of lung cancer in current smokers and the higher risk in non-smokers. The lower lifetime consumption of cigarettes in Japanese, due partly to the later initiation of smoking habits, the lower consumption per day, or the shortage of cigarettes during and immediately after World War II in Japan, may be one explanation for the lower risk of lung cancer in Japanese smokers. However, the differences in other factors, including ingredients and filters of cigarettes, lifestyle factors other than smoking and genetic susceptibility to lung cancer between Japanese and Western populations, should also be considered when explaining the lower risk among Japanese (1,2).

Table 4. Summary table of the association between tobacco smoking and lung cancer risk in case–control studies among Japanese population

Reference	Study period	Study subjects				Magnitude of association[a]
		Sex	Age (years)	Number of cases	Number of controls	
Nakamura et al. (14)	1978–82	Men	NA	498	498	↑↑↑
		Women	NA	84	84	↑↑
Shimizu et al. (15)	1977–82	Men	40+	603	727	↑↑↑
		Women	40+	148	746	↑↑↑
Tsugane et al. (16)	1976–85	Men	30–49	93	93	↑↑↑
		Women	30–49	41	41	↓
Sakai (17)	1982–86	Men and women	30+	64	128	↑↑↑
		Men	30+	41	82	↑↑↑
Minowa et al. (18)	1978–82	Men	NA	96	86	↑↑↑
Yamaguchi et al. (19)	1989–90	Men and women	NA	144	676	↑↑↑
Gao et al. (20)	1988–91	Men	30–84	282	282	↑↑↑
Shimizu et al. (21)	1973–91	Men	40+	413	82	↑↑↑
		Women	40+	192	101	↑↑↑
Sobue et al. (22)	1986–88	Men	40–79	1052	1111	↑↑↑
		Women	40–79	294	1089	↑↑↑
Wakai et al. (23)	1988–91	Men	40–89	245	490	↑↑↑
		Women	40–89	88	176	↑↑↑
Stellman et al. (24) (Aichi portion)	1993–98	Men	20–81	410	252 (hospital controls)	↑↑↑
		Men	20–81	410	411 (community controls)	
Ito et al. (25)	1999–2000	Men and women	26–80	138 (adenocarcinoma)	241	–
Minami et al. (26)	1997–2001	Men	40+	354	1222	↑↑↑
		Women	40+	161	1222	↑↑↑
Marugame et al. (27)	1996–98	Men	40–79	839	491	↑↑↑
		Women	40–79	316	389	↑↑↑

NA, not available.
[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; –, no association (see Methods for a more detailed definition).

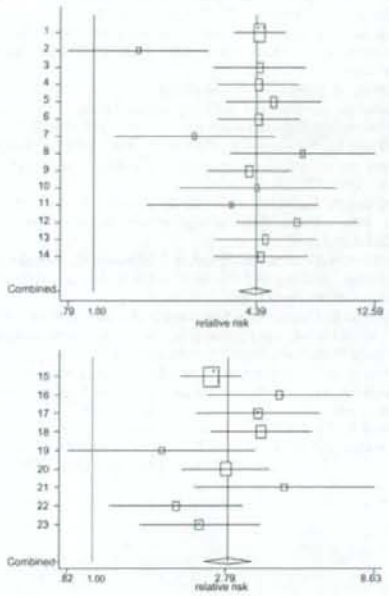
In addition to the summary measures for all lung cancer, we estimated the summary RRs (current smokers versus never smokers) by histological type by using the meta-analysis method mentioned above. In men, the resultant summary RRs were 11.7 (95% CI 8.31–16.6) for squamous cell carcinoma, 2.30 (95% CI 1.89–2.79) for adenocarcinoma and 14.0 (95% CI 6.64–29.4) for small cell carcinoma. In women, they were 11.3 (95% CI 7.15–17.9) for squamous cell carcinoma and 1.37 (95% CI 1.08–1.76) for adenocarcinoma. [The RRs for large cell carcinoma and female small cell carcinoma were not estimated due to the small number of studies (one or two) reporting required data].

In the IARC evaluation (7), it was concluded that the major cause of human lung cancer is tobacco smoking. The evaluation also noted that exposure to tobacco smoke led to modest increases in the occurrence of malignant and/or benign lung tumors in rats and mice and that smoking-related DNA adducts were detected in the respiratory tract. We therefore assumed that the association of tobacco smoking with lung cancer risk held biological plausibility.

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

Based on these results and assumed biological plausibility, we conclude that there is convincing evidence that tobacco smoking strongly increases the risk of lung cancer in the Japanese population. The RR for Japanese current smokers compared with never smokers was estimated to be around 4.4 for men and 2.8 for women. These figures can be used to plan programs for the primary prevention of lung cancer by the reduction of tobacco smoking in Japan.

No.	First author	Year	Ref. No.	Sex	Design	Event	RR for current versus never smokers (95%	
Men								
1	Akiba S	1990	(10)	M	CH	Death	4.50	(3.60- 5.70)
2	Tomita M	1991	(11)	M	CH	Death	1.50	(0.79- 2.83) *
3	Sobue T	2002	(1)	M	CH	Incidence	4.50	(3.00- 6.80)
4	Ando M	2003	(3)	M	CH	Death	4.46	(3.10- 6.41)
5	Marugame T	2005	(2)	M	CH	Death	5.10	(3.34- 7.79)
6	Nakamura M	1986	(14)	M	CC		4.47	(3.10- 6.46) *
7	Sakai R	1989	(17)	M	CC		2.50	(1.20- 5.10)
8	Gao CM	1993	(20)	M	CC		6.61	(3.47- 12.58)
9	Sobue T	1994	(22)	M	CC		4.10	(2.80- 5.90)
10	Wakai K	1997	(23)	M	CC		4.40	(2.19- 8.85)
11	Stellman SD	2001	(24)	M	CC		3.50	(1.60- 7.50)
12	Stellman SD	2001	(24)	M	CC		6.30	(3.70- 10.90)
13	Minami Y	2003	(26)	M	CC		4.75	(3.04- 7.42)
14	Marugame T	2004	(27)	M	CC		4.56	(3.00- 6.94)
Women								
15	Akiba S	1990	(10)	F	CH	Death	2.50	(2.00- 3.20)
16	Sobue T	2002	(1)	F	CH	Incidence	4.20	(2.40- 7.20)
17	Ando M	2003	(3)	F	CH	Death	3.58	(2.24- 5.73)
18	Marugame T	2005	(2)	F	CH	Death	3.66	(2.50- 5.35)
19	Nakamura M	1986	(14)	F	CC		1.70	(0.80- 3.40)
20	Sobue T	1994	(22)	F	CC		2.80	(2.00- 3.90)
21	Wakai K	1997	(23)	F	CC		4.37	(2.21- 8.62)
22	Minami Y	2003	(26)	F	CC		1.91	(1.14- 3.18)
23	Marugame T	2004	(27)	F	CC		2.29	(1.44- 3.64)



Summary estimates (fixed-effect model)				
	Men	Total	4.39	(3.92- 4.92) (Test for heterogeneity: Q=17.681 with df=13, P=0.170)
		Cohort studies	4.28	(3.65- 5.00) (Test for heterogeneity: Q=11.357 with df=4, P=0.023)
		Case-control studies	4.52	(3.83- 5.32) (Test for heterogeneity: Q=6.106 with df=8, P=0.635)
	Women	Total	2.79	(2.44- 3.20) (Test for heterogeneity: Q=12.271 with df=8, P=0.139)
		Cohort studies	3.00	(2.52- 3.57) (Test for heterogeneity: Q=5.347 with df=3, P=0.148)
		Case-control studies	2.51	(2.02- 3.11) (Test for heterogeneity: Q=5.316 with df=4, P=0.256)

RR, Relative risk; CI, confidence interval; CH, cohort study; CC, case-control study; M, male; F, female.

Boxed area represents the contribution of each study (weight) to the meta-analysis.

*RRs and 95% CIs of references (11) and (14) were estimated from those estimated for daily amount of smoking categories or those estimated for cell type by meta-analysis.

References (12), (16), and (18) were excluded from the meta-analysis since point estimates and/or confidence intervals were not available or could not be estimated from other given values.

References (13), (19), and (25) were excluded because only findings for men and women combined were reported.

References (9), (15), and (21) were excluded because the reference group included both never and former smokers

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

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