It will therefore be of importance to quantify the impact of smoking on the development of lung cancer using data from Japanese populations in order for us to estimate how much of a decrease in the incidence or mortality of lung cancer can be expected by reducing the smoking prevalence in this country. Fortunately, large prospective studies have recently provided highly reliable evidence for the association between smoking and lung cancer risk, thus making a more accurate assessment possible. Such studies include the Three-Prefecture Cohort Study (2), the Japan Collaborative Cohort Study (3) and the Japan Public Health Center-based Prospective Study (1).

In the present study, we evaluated the magnitude of the association between tobacco smoking and the risk of lung cancer among Japanese by conducting a systematic review of epidemiological evidence to provide the basic data for the primary prevention of lung cancer in Japan. This report is one among a series of articles by our research group, which is investigating the association between health-related lifestyles (e.g. tobacco smoking, alcohol consumption and diet) and the risk of total cancers and major cancer sites (i.e. the stomach, colon and rectum, liver, lung and breast) in Japan (4,5).

METHODS

The original data for this review were identified by searches of MEDLINE using PubMed, supplemented with manual searches of references from relevant articles where necessary. All epidemiological studies on the association between tobacco smoking and lung cancer incidence or mortality among Japanese from 1968 to 2005 were identified using the search terms 'smoking', 'lung cancer', 'cohort studies', 'case–control studies' and 'Japan' as keywords found in the abstract. Papers published in either English or Japanese were reviewed, and only studies on Japanese populations residing in Japan were included. In the case of multiple publication of the same or overlapping datasets, only data from the latest or most comprehensive results were included. The individual results were summarized separately in the tables by a study design as cohort or case–control studies.

We evaluated the results based on the magnitude of association and the strength of evidence. First, the RRs by gender in each epidemiological study were grouped by magnitude of association, with consideration for statistical significance (SS) or no statistical significance (NS), as strong (symbol ↑↑↑ or ↓↓↓), <0.5 or >2 (SS); moderate (symbol ↑↑ or ↓↓), (1) <0.5 or >2 (NS), (2) >1.5 to 2 (SS) or (3) 0.5 to <0.67 (SS); weak (symbol ↑ or ↓), (1) >1.5 to 2 (NS), (2) 0.5 to <0.67 (NS) or (3) 0.67 to 1.5 (SS); or no association (symbol —), 0.67 to 1.5 (NS). The RR was approximated by the odds ratio in case–control studies. When the amount smoked was grouped into several levels or subgroup analyses by cell type were made, we considered the highest RR or odds ratio among all the exposure levels or subgroups.

After this process, the strength of evidence was evaluated in a similar manner to that used in the WHO/FAO Expert Consultation Report (6), in which evidence was classified as 'convincing', 'probable', 'possible' or 'insufficient', based on a consensus of the research group members. We assumed that biological plausibility corresponded to the judgment of the most recent evaluation from the International Agency for Research on Cancer (IARC) (7). The details underlying those judgments have been described elsewhere (4,5).

In addition, when we reached a conclusion that there was 'convincing' or 'probable' evidence of an association, a meta-analysis was conducted to obtain summary estimates for the overall magnitude of association. In principle, studies that reported RRs or odds ratios and their confidence intervals (CIs) by comparing current smokers with never smokers were included in the meta-analysis. For those that categorized risk values separately according to the smoking amount, such as the number of cigarettes smoked per day or the pack-year index, we first conducted a meta-analysis to estimate summary risk values for current smokers and then used these values for further meta-analysis. Studies without information on CIs of risk estimates or those with a reference group other than a group of never smokers were excluded from the meta-analysis. General variance-based methods were used to estimate summary statistics and their 95% CIs. Heterogeneity among studies was tested using the Q statistic together with a model to determine the summary RR and its 95% CI, i.e. a random- or fixed-effect model, selected according to the statistical significance in the Q statistic. The meta-analysis was performed using the *meta* command of the STATA statistical package (Stata Corporation, College Station, TX, USA), version 8 (8).

MAIN FEATURES AND COMMENTS

A total of 8 cohort studies (1–3,9–13) and 14 case–control studies (14–27) were identified (Tables 1 and 2, respectively). Of the eight cohort studies, three (1,2,10) were population-based, in which subjects were recruited from general populations in geographically defined areas with a high response rate (>80%). The endpoint was defined as incidence of lung cancer in three studies (1,12,13) and death due to cancer in other cohort studies (2,3,9–11). The follow-up rate exceeded 90% in all the studies reporting the follow-up status of participants (1,3,9–11), except for one study in which 15.6% of the subjects migrated from the study areas (2).

All the identified case–control studies were hospital-based, that is cases were enrolled in arbitrarily selected hospitals. In all (14,16–22,25–27) but three investigations (15,23,24) control subjects were also selected from patients in the hospitals where cases arose (hospital controls). Two studies (15,23) included controls randomly sampled from general populations (population or community controls). Stellman et al. (24) adopted both hospital and community controls. The diagnosis of cases was microscopically confirmed in most of the studies (14–16,18,19,21–25,27), and the response rate was reasonably high (at least 70%) in studies reporting the relevant figures among cases (14,15,18,21,23,24) and/or controls (15,18,21,24).

Table 1. Tobacco smoking and lung cancer risk in cohort studies among Japanese population

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI or P)	P for trend	Confounding variables considered
		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths					
Kono et al. (9)	1965–83	5130 men	Membership lists of 9 prefectural medical associations	Death	74 men	Never or past		1.00		Age and alcohol drinking
						Current 1–19 cigarettes/day		3.18 (1.57–6.45)		
						20+		8.15 (4.12–16.10)		
Akiba and Hirayama (10)	1966–81	122 261 men—α	95% of census population	Death	1200 men	Never	80	1.0		Age, residence, occupation, and observation period
						Current	1120	4.5 (3.6–5.7)		
						1–4 cigarettes/day	14	2.5 (1.4–4.3)		
						5–14	361	3.3 (2.6–4.3)		
						15–24	629	5.4 (4.3–6.9)		
						25–34	76	7.1 (5.1–9.7)		
						35+	40	8.4 (5.7–12.3)	$P < 0.001$	
		142 857 women—α			394 women	Never	303	1.0		
						Current	91	2.5 (2.0–3.2)		
						1–4 cigarettes/day	11	1.9 (1.0–3.2)		
						5–14	65	2.5 (1.9–3.3)		
						15+	15	3.1 (1.8–5.1)	$P < 0.001$	
Tomita et al. (11)	1975–85	37 645 men	Male employees of a railway company	Death	32 men	Never Past	5 5	1.00 1.73 (0.09–11.3)		Age and observation period
						Current 1–14 cigarettes/day	2	0.89 (0.13–3.1)		
						15–24	8	0.81 (0.27–2.7)		
						25–34	8	2.36 (0.79–7.8)		
						35+	4	2.72 (0.67–10.3)	$P < 0.1$	
Murata et al. (12)	1984–93	107 male cases and 214 controls (nested case–control study)	17 200 male participants in a gastric mass screening	Incident cases	107 men	Never or past	31	1.0		Matched (1:2) for: birth year (±2 years) and address
						Current 1–10 cigarettes/day	9	1.4 (NS)		
						11–20	47	3.6 ($P < 0.01$)		

Table 1. *Continued*

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI or P)	P for trend	Confounding variables considered
		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths					
						21+	20	4.6 ($P < 0.01$)	$P < 0.01$	
Sobue et al. (1)	1990–99	44 533 men	Residential registry	Incident cases	324 men	Never	26	1.0		Age and area
						Past	67	2.2 (1.4–3.4)		
						Current	231	4.5 (3.0–6.8)		
						0–19 cigarettes/day	60	1.0		
						20–29	105	1.2 (0.9–1.7)		
						30–39	32	1.4 (0.9–2.2)		
						40+	26	1.6 (1.0–2.6)	$P = 0.03$	
					133 male cases of SQ+SM	Never	4	1.0		
						Past	25	5.1 (1.8–14.6)		
						Current	104	12.7 (4.7–34.7)		
					119 male cases of AD	Never	15	1.0		
						Past	23	1.3 (0.7–2.5)		
						Current	81	2.8 (1.6–4.9)		
		48 281 women			98 women	Never	78	1.0		
						Past	4	3.7 (1.4–10.2)		
						Current	16	4.2 (2.4–7.2)		
					11 female cases of SQ+SM	Never	5	1.0		
						Past	1	10.8 (1.2–94.4)		
						Current	5	17.5 (4.9–62.1)		
					62 female cases of AD	Never	54	1.0		
						Past	3	4.3 (1.3–13.8)		
						Current	5	2.0 (0.8–5.0)		
Pierce et al. (13)	1958–94	45 113 men and women	Atomic-bomb survivors	Incident cases	592 men and women	Never or past		1.0		Age, sex, birth cohort, and radiation dose
						Current 1–15 cigarettes/day		4.9 (0.8–9.0)		
						16–25		8.0 (0.6–15.4)		
						26+		13.3 (1.0–25.6)		
						(Smoking level for those age 30 in 1945 and for attained age 60–70)				

Ando et al. (3)	1988–97	45 010 men	Participants in health check-ups or general population	Death	469 men	Never	32	1.00		Age
						Past	120	2.38 (1.61–3.51)		
						Current	317	4.46 (3.10–6.41)		
						0–9 cigarettes/day	10	2.3 (1.1–4.6)		
						10–19	76	3.2 (2.1–4.8)		
						20–29	146	5.2 (3.5–7.6)		
						30+	71	7.9 (5.2–12.0)		
		55 724 women			128 women	Never	101	1.00		
						Past	6	2.56 (1.12–5.83)		
						Current	21	3.58 (2.24–5.73)		
Marugame et al. (2)	1983–2000	44 451 men	Residential registry	Death	466 men	Never	23	1.00		Age and prefecture
						Past	102	2.60 (1.65–4.10)		
						Current	341	5.10 (3.34–7.79)		
						0–19 pack-years	19	1.16 (0.72–1.88)		
						20–39	113	2.10 (1.62–2.71)		
						40–59	129	2.86 (2.23–3.65)		
						60+	78	4.44 (3.34–5.89)	$P < 0.0001$	
		43,702 women			132 women	Never	79	1.00		
						Past	13	2.94 (1.63–5.31)		
						Current	40	3.66 (2.50–5.35)		
						0–19 pack-years	12	1.75 (0.96–3.19)		
						20–39	15	3.92 (2.27–6.76)		
						40+	10	7.22 (3.75–13.9)	$P < 0.0001$	

CI, confidence interval; SQ, squamous cell carcinoma; SM, small cell carcinoma; AD, adenocarcinoma; NS, not statistically significant. 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.

Table 2. Tobacco smoking and lung cancer risk in case–control studies among Japanese population

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				
Nakamura et al. (14)	1978–82	Hospital-based (Center for Adult Diseases, Osaka)	Cases: histologically confirmed; Controls: outpatients without definite or suspected lung cancer	174 male cases of SQ	174 men	Never	1.0		Matched (1:1) for: sex, age (exactly), and date of first visit (±3 months)
						Past	3.7 (1.6–8.5)		
						Current	6.0 (3.1–11.5)		
				84 male cases of SM	84 men	Never	1.0		
						Past	5.4 (1.4–20.8)		
						Current	10.3 (3.9–27.4)		
				198 male cases of AD	198 men	Never	1.0		
						Past	1.7 (0.8–3.7)		
						Current	2.8 (1.6–4.8)		
				42 male cases of LA	42 men	Never	1.0		
						Past	1.5 (0.2–9.3)		
						Current	4.4 (1.3–14.5)		
				84 female cases of AD	84 women	Never	1.0		
						Past	3.0 (0.6–14.9)		
						Current	1.7 (0.8–3.4)		
Shimizu et al. (15)	1977–82	Hospital-based (Sendai Kosei Hospital)	Cases: microscopically confirmed; Controls: randomly selected residents	603 men	727 men	Never + past	1.0		Age and residence
						Current	3.7 (2.7–5.1)		
				171—α male cases of AD	727 men	Never + past	1.0		
						Current	1.9 (1.3–3.0)		
				281—α male cases of SQ	727 men	Never + past	1.0		
						Current	4.3 (2.8–6.7)		
				104—α male cases of SM	727 men	Never + past	1.0		
						Current	3.9 (2.0–7.7)		
				82—α male cases of LA	727 men	Never + past	1.0		
						Current	3.4 (1.8–6.7)		
				148 women	746 women	Never + past	1.0		
						Current	3.4 (2.1–5.3)		
				99—α female cases of AD	746 women	Never + past	1.0		
						Current	2.9 (1.7–5.0)		
				18—α female cases of SQ	746 women	Never + past	1.0		
						Current	6.4 (2.3–17.3)		
				27—α female cases of SM	746 women	Never + past	1.0		
						Current	4.5 (1.8–10.9)		

				18—α female cases of LA	746 women	Never + past	1.0	
						Current	4.0 (1.6–10.3)	
Tsugane et al. (16)	1976–85	Hospital-based (National Cancer Center)	Cases: histologically confirmed cases aged 30–49; Controls: cancer-free patients	73 male cases of AD	73 men	Never	1.00	Matched (1:1) for: sex, age (±2 years), year of admission (±1 year), and residence
						Ever	0.89 (NS)	
						Never + past	1.00	
						Current	0.80 (NS)	
				41 female cases of AD	41 women	Never	1.00	
						Ever	0.55 (NS)	
						Never + past	1.00	
						Current	0.55 (NS)	
				20 male cases of SQ	20 men	Never	1.00	
						Ever	Infinite ($P < 0.05$)	
						Never + past	1.00	
						Current	4.85 (NS)	
Sakai (17)	1982–86	Hospital-based (5 hospitals in Naha City)	Cases: incident cases; Controls: patients without a history of cancer, COPD, etc.	64 men and women	128 men and women	Never	1.0	Matched (1:2) for: sex and age (±5 years)
						Current	2.9 (1.6–5.3)	
				41 men	82 men	Never	1.0	
						Past	6.3 (1.9–21.0)	
						Current	2.5 (1.2–5.1)	
						1–19 cigarettes/day	4.3 (1.3–13.5)	
						20	3.3 (0.9–4.6)[a]	
						20+	4.5 (1.5–13.2)	
Minowa et al. (18)	1978-1982	Hospital-based (Yokosuka Kyosai Hospital)	Cases: microscopically confirmed fatal cases; Controls: fatal cases without cancer or pneumo-coniosis	96 men	86 men	Never	1.00	Matched (1:1) for: date of birth (nearest)
						Past	7.69 ($P < 0.05$)	
						Current	6.52 ($P < 0.01$)	
						Never	1.00	
						Ever 1–19 cigarettes/day	6.78 ($P < 0.01$)	
						20+	6.42 ($P < 0.01$)	
Yamaguchi et al. (19)	1989–90	Hospital-based (3 hospitals in Kitakyushu City)	Cases: histologically confirmed; Controls: hospitalized patients without lung cancer	144 men and women	676 men and women	Never	1.00	Matched for: hospital, sex, and age (5 year group); Adjusted for job categories
						Past	2.90 (1.43–5.90)	
						Current 1–20 cigarettes/day	3.75 (1.89–7.47)	
						21+	12.14 (5.10–28.90)	

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				
Gao et al. (20)	1988–91	Hospital-based (Aichi Cancer Center)	Cases: incident cases; Controls: patients without cancer	282 men	282 men	Never	1.00		Matched (1:1) for: age (±1 year), and time of first visit to the hospital (±30 days)
						Past	3.56 (1.83–6.91)		
						Current	6.61 (3.47–12.58)		
						1–19 cigarettes/day	3.46 (1.57–7.19)		
						20–29	7.53 (3.71–15.30)		
						30+	10.63 (5.08–22.22)		
Shimizu et al. (21)	1973–91	Hospital-based (Cancer Institute)	Cases: patients with SQ or AD who underwent surgical resection; Controls: patients with metastatic lung cancer	194 male cases of SQ	82 men	Never	1.0		Age
						Ever	12.8 (5.1–32.3)		
				10 female cases of SQ	101 women	Never	1.0		
						Ever	7.4 (2.2–25.5)		
				219 male cases of AD	82 men	Never	1.0		
						Ever	1.5 (0.8–2.9)		
				182 female cases of AD	101 women	Never	1.0		
						Ever	1.1 (0.6–1.9)		
Sobue et al. (22)	1986–88	Hospital-based (8 hospitals in Osaka Prefecture)	Cases: microscopically confirmed; Controls: hospitalized patients without established smoking-related diseases	1082 men	1141 men	Never	1.0		Age (for all subjects), duration of smoking, number of cigarettes smoked per day, fraction smoked per cigarette, cigarette type (filter or non-filter), and inhalation (for male current smokers only)
						Past	2.8 (1.9–4.2)		
						Current	4.1 (2.8–5.9)		
						1–19 cigarettes/day	1.0		
						20–29	1.3 (1.0–1.8)		
						30+	1.7 (1.2–2.3)		
				425 male cases of SQ	1141 men	Never	1.0		
						Past	13.1 (5.2–33.4)		
						Current	18.1 (7.9–41.3)		
				420 male cases of AD	1141 men	Never	1.0		
						Past	1.5 (0.9–2.4)		
						Current	1.9 (1.3–3.0)		
				130 male cases of SM	1141 men	Never	1.0		
						Past	9.2 (1.5–56.8)		
						Current	21.4 (5.3–87.1)		
				81 male cases of LA	1141 men	Never	1.0		
						Past	2.6 (0.7–10.0)		
						Current	3.8 (1.2–12.1)		

				294 women	1089 women	Never	1.0	
						Past	2.1 (1.4−3.2)	
						Current	2.8 (2.0−3.9)	
				50 female cases of SQ	1089 women	Never	1.0	
						Past	5.6 (2.3−13.8)	
						Current	9.7 (5.5−16.8)	
				195 female cases of AD	1089 women	Never	1.0	
						Past	1.7 (1.0−3.0)	
						Current	1.3 (0.9−2.0)	
				35 female cases of SM	1089 women	Never	1.0	
						Past	4.7 (1.3−17.4)	
						Current	12.1 (6.3−23.4)	
				14 female cases of LA	1089 women	Never	1.0	
						Past	4.1 (1.4−32.8)[a]	
						Current	3.7 (1.1−11.7)	
Wakai et al. (23)	1988–91	Hospital-based (National Okinawa Hospital)	Cases: histologically confirmed; Controls: randomly selected residents	245 men	490 men	Never	1.00	Matched (1:2) for: sex, age (±2 years), and residence
						Past	2.43 (1.16−5.06)	
						Current	4.40 (2.19−8.85)	
						1−19 cigarettes/day	1.80 (0.81−4.02)	
						20−29	4.01 (1.91−8.41)	
						30+	9.19 (4.20−20.1)	
				115 male cases of SQ	490 men	Never	1.00	
						Past	6.16 (1.42−26.7)	
						Current	9.82 (2.36−41.0)	
				106 male cases of AD	490 men	Never	1.00	
						Past	1.40 (0.59−3.31)	
						Current	2.18 (1.00−4.76)	
				88 women	176 women	Never	1.00	
						Past	5.33 (1.21−23.5)	
						Current	4.37 (2.21−8.62)	
				19 female cases of SQ	176 women	Never	1.00	
						Past	9.76 (0.85−112)	
						Current	28.2 (7.55−105)	
				59 female cases of AD	176 women	Never	1.00	
						Past	2.69 (0.68−10.6)	
						Current	1.14 (0.49−2.61)	

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) (Aichi portion)	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)		
						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).

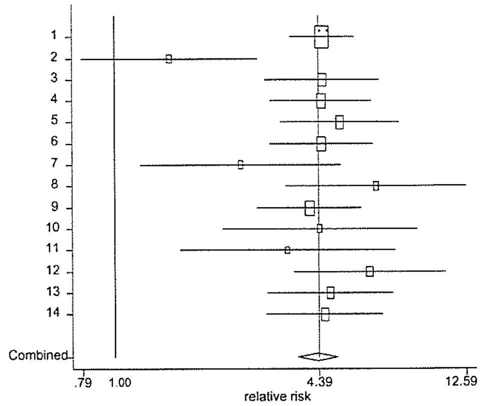
In addition to the summary measures for all lung cancer, we estimated the summary RRs (current smokers versus never smokers) by histological type by using the meta-analysis method mentioned above. In men, the resultant summary RRs were 11.7 (95% CI 8.31–16.6) for squamous cell carcinoma, 2.30 (95% CI 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].

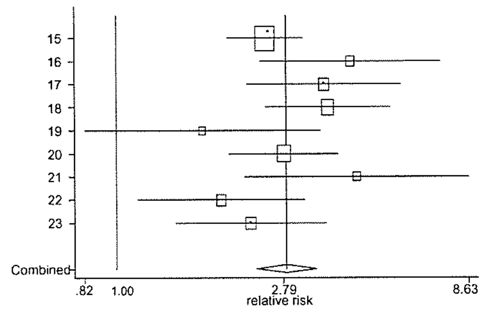
In the IARC evaluation (7), it was concluded that the major cause of human lung cancer is tobacco smoking. The evaluation also noted that exposure to tobacco smoke led to modest increases in the occurrence of malignant and/or benign lung tumors in rats and mice and that smoking-related DNA adducts were 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.

Study				Sex	Design	Event	RR for current versus never smokers (95%	
No.	First author	Year	Ref. No.					
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)

		RR	(95% CI)	
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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Tobacco Smoking and Breast Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiological Evidence among the Japanese Population

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Background: Our research group undertook an appraisal of the body of epidemiological studies on cancer in Japan to evaluate the existing evidence concerning the association between health-related lifestyles and cancer. As tobacco smoking may be one of the few modifiable risk factors for breast cancer, we focused on the association between tobacco smoking and the risk of breast cancer in this review.
Methods: A MEDLINE search was conducted to identify epidemiological studies on the association between smoking and breast cancer incidence or mortality among the Japanese from 1966 to 2005. 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: Three cohort studies and eight case-control studies were identified. The relative risk (RR) or odds ratio (OR) of breast cancer for current smokers ranged from 0.71 to 6.26 in these studies. A significantly increased risk among current smokers compared with never smokers (RR = 1.7) was reported in one out of the three cohort studies. Moderate or strong associations between smoking and breast cancer risk (OR > 2.0) were observed in four of the eight case-control studies. Experimental studies have supported the biological plausibility of a positive association between tobacco smoking and breast cancer risk.
Conclusion: We conclude that tobacco smoking possibly increases the risk of breast cancer in the Japanese population.

Key words: systematic review – epidemiology – tobacco smoking – breast cancer – the Japanese

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in women, the incidence rate of which has increased considerably among Japanese women in recent years. The established risk factors include menstrual and reproductive history, family history of breast cancer, postmenopausal obesity, genetic susceptibility and exposure to ionizing radiation (1). Yet more than half of breast cancer risk remained unexplained. Our research group undertook an appraisal of the body of epidemiological studies on cancer in Japan to evaluate the existing evidence concerning the association between health-related lifestyles and cancer (2). Tobacco smoking may be one of the few modifiable risk factors for breast cancer. The following is a summary of information from epidemiological studies on smoking and breast cancer.

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METHODS

A MEDLINE search was conducted to identify epidemiological studies on the association between smoking and breast cancer incidence or mortality among the Japanese from 1966 to 2005. Papers written in either English or Japanese were reviewed, and only studies on the Japanese populations living in Japan were included.

Individual results were summarized in tables separately by study design as cohort or case-control studies. Relative risks (RRs) or odds ratios (ORs) 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 to 2 (SS), or (iii) 0.5 to <0.67 (SS); weak, either (i) >1.5–2.0 (NS), (ii) 0.5 to <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 in the WHO/FAO Expert Consultation Report (3), 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 the International Agency for Research on Cancer (IARC) (4). 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 incidence was given priority over mortality as an outcome measure. Details on the evaluation methods are described elsewhere (2).

MAIN FEATURES AND COMMENTS

We identified three cohort studies (5–7) and eight case-control studies (8–15). Besides these studies, two case-control studies (16,17) referred to the association between smoking and breast cancer risk in addition to their main findings. However, they were not included in this review because the data overlapped with those used for previous study conducted by the same institute. Details of the component studies including age range, study period, numbers of women enrolled, RR or OR of breast cancer for smoking status or/and number of cigarettes smoked per day and years of smoking, and covariates used in adjustment are described in Tables 1 and 2. Summaries of the magnitudes of association for these studies are shown in Tables 3 and 4.

Among the three cohort studies, a significantly increased risk among current smokers compared with never smokers was reported in one study (RR = 1.7) (7) but not in the others (Table 1). The RRs for current vs. never/non-smokers were 1.28 and 0.97 in the other two studies, respectively.

Moderate or strong associations between smoking and breast cancer risk were observed in four of the eight case-control studies (11–14). The ORs of breast cancer for current or ex-smokers reported from the case-control studies ranged from 0.71 to 6.26. All the case-control studies were hospital-based except one study by Ueji et al. (14). This study reported the highest OR for current smokers. The response rates from cases and community controls were 75.5 and 67.4%, respectively in the study.

As alcohol drinking and smoking are closely associated, there is potential for confounding of alcohol use on the association between smoking and breast cancer. One of the three cohort studies (7) and two of the eight case-control studies reported associations after adjustment for alcohol use (9,15). However, in most of the other studies, information on alcohol use was obtained. Authors did not observe confounding effect of alcohol on the association between smoking and breast cancer risk. Some but not all studies took account of other known risk factors of breast cancer, such as parity, age at menarche, age at first birth, age at menopause and family history of breast cancer. However, the studies showing RRs/ORs with and without adjustment for these factors (7,8,13–15) revealed that the association between smoking and breast cancer was not substantially altered.

Tobacco smoking has been suggested as a cause of breast cancer. In the evaluation of IARC (4), smoking and tobacco smoke are judged to be carcinogenic to humans. Chemical carcinogens in tobacco smoke can cause mammary tumors in animals (4,18). Metabolites of tobacco smoke have been formed in the breast fluid or tissue of smokers (19,20). Thus, it is biologically plausible that exposure to tobacco smoke is related to breast cancer. However, epidemiological studies of smoking and breast cancer have produced inconsistent results (4,21–23). A recent pooled analysis of 53 epidemiological studies showed no increased risk of breast cancer associated with smoking (24). However, passive smoking has been suggested to be associated breast cancer risk rather consistently (23). Thus, the risk of active smoking may be canceled out by the passive smoking risk in the control group. Some studies suggested that longer duration or high intensity of smoking may be associated with an increased risk of breast cancer (25,26). Studies referring to years of smoking, age at smoking started or pack-years of smoking were few in the present review and implications of these factors in breast cancer risk among Japanese women were equivocal.

Unlike the previous reviews of studies among non-Japanese populations, the present review indicates a positive association between smoking and breast cancer. We have no explanation for this difference at this moment. It is unlikely that female smokers in Japan smoke more heavily and have a longer duration of smoking. Marugame et al. (27) reported that both the number of years of smoking and the number of cigarettes smoked per day were lower among Japanese smokers than those observed for smokers of both sexes in the USA. Differences in endogenous estrogen status or distribution of certain genes related to metabolic enzymes among populations may partially explain the discrepancy between the present and previous reviews. Any antiestrogenic effects of smoking may be smaller in women with low circulating estrogen levels as in the case of postmenopausal Japanese women. However, there was no consistent interaction with menopausal status in the present and previous reviews (22). Certain genotypes, such as GSTT1-null (28,29), XPD-Gly/Gly (30,31), XRCC1 Arg399Gln/Gln (31,32), CYP1A1*2A (33,34) and slow NAT2 genotypes (29,35) have been suggested to increase the risk of breast cancer

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

References: Author	References: Year	Study period	Study population Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths	Category	Number among cases	Relative risk (95%CI)	p for trend	Confounding variables considered
Hirayama (5)	1990	1966–1982	142,857	Census-based 6 prefecture	Mortality	241	Non-smoker		1.00		Adjusted for age
							Daily smoker		1.28 (0.93–1.76)		
							No. of cigarettes smoked				
							1–9		0.94 (0.56–1.60)		
							10–19		1.38 (0.85–2.23)		
							20+		1.03 (0.30–3.48)		
							Age at start of smoking				
							<20		1.39 (0.26–7.58)		
							>0+		1.17 (0.80–1.71)		
Goodman et al.	1997	1979–1987	22,200	RERF Life Span Study Cohort (a-bomb survivors)	Incidence	161	Never smokers	135	1.00		Adjusted for city, age, age at the time of the bombings, and radiation dose to the breast
							Ever smokers	21	0.78 (0.49–1.24)		
							Ex-smokers	2	0.32 (0.08–1.28)		
							Present smokers	19	0.97 (0.60–1.58)		
				Tumor registry at the RERF			Pack-years				
							<10	9	1.41 (0.71–2.76)		
							⩾10	8	0.52 (0.25–1.06)	0.11	
Hanaoka et al.	2005	1990–1999	21,805	JPHC study	Incidence	180	Never smokers	162	1.00		Adjusted for public health center, age, education level, BMI, family history of breast cancer in mother or sisters, history of past benign breast disease, age at menarche, number of births, menopausal status, hormone use and alcohol consumption
							Ex-smokers	4	1.1 (0.4–3.6)		
							Current smokers	14	1.7 (1.0–3.1)		

RERF, the Radiation Effects Research Foundation: JPHC, the Japan Public Health Center-Based (JPHC) Study.

Table 2. Tobacco smoking and breast cancer risk, case-control study in Japanese population

References: Author	References: year	Study time	Study subjects: Type and source	Definition	Number of cases	Number of controls	Category (smoking)	Odds ratio (95%CI)	p for trend	Confounding variables considered
Hirohata et al.	1985	Not specified	Hospital-based (National Kyushu Cancer Center, Kyusyu Univ, Fukuoka Univ, Kurume Univ, National Fukuoka Central Hospital)	Cases: histologically confirmed cases; Controls: hospital control without history of cancer and benign breast disease, neighborhood control	212	424	Never	1.00		Matched (1:2) for age (±5 yrs); Adjusted for family history of cancer, history of benign breast disease, hysterectomy, abnormal menses, induced or natural abortion, age at menarche, age at first birth and exogenous estrogen use
							Ever	0.80 (0.50–1.29)		
Kato et al.	1989	1980–1986	Hospital-based (Achi Cancer Registry)	Cases: histologically confirmed cases; Controls: hospital control	1,740	8,920	Never	1.00		Adjusted for age, alcohol drinking, marital status, residence, occupation and family history of breast cancer
							Current	0.87 (0.74–1.02)		
Kato et al.	1992	1990–1991	Hospital-based (10 large hospitals in eight prefectures)	Cases: histologically confirmed cases; Controls: hospital controls without hormone-related cancers	908	908	Non-smokers	1.00		Matched (1:1) for age (±3 yrs) and hospital
							Smokers	1.20 (0.92–1.57)		
Wakai et al.	1994	1990–1991	Hospital-based (Cancer Institute Tokyo)	Cases: histologically confirmed cases; Controls: patients without breast cancer	300	900	Never	1.00		Matched (1:1) for age
							Ex-smokers	0.91 (0.49–1.70)		
							Current	1.63 (1.11–2.39)		Adjusted for menopausal status, weight, height, lactation and no. of births
					168 premenopausal	472 premenopausal	Never	1.00		
							Ex-smokers	0.96 (0.42–2.20)		
							Current	1.23 (0.75–2.03)		
					127 postmenopausal	390 postmenopausal	Never	1.00		
							Ex-smokers	0.80 (0.28–2.32)		
							Current	2.73 (1.38–5.39)		
Hirose et al.	1995	1988–1992	Hospital-based (Aichi Cancer Center)	Cases: histologically confirmed cases; Controls: first-visit outpatients without history of cancer	1186	23 163				Adjusted for age and first-visit year
					607 premenopausal	15,084 premenopausal	Never	1.00		
							Smokers	1.35 (1.09–1.68)		
							<10/day	1.50 (1.04–2.17)		
							>=10/day	1.31 (1.02–1.69)		
					445 postmenopausal	6215 postmenopausal	Never	1.00		
							Smokers	1.10 (0.80–1.51)		
							<10/day	0.82 (0.38–1.77)		
							>=10/day	1.13 (0.79–1.61)		

Hu	1997	1989–1993	Hospital-based (Gihoku General Hospital)	Cases: histologically confirmed cases; Controls: participants in breast cancer screening	157	369	Never	1.00	Matched for age and residential area
							Ex- or current smokers	2.31 (1.19–4.49)	Adjusted for BMI, age at menarche, age at first birth, no. of births and duration of breast-feeding
Uegi et al.	1998	1990–1997	Tsukuba Univ Hospital, Tsukuba Medical Center Hospital Community controls	Cases: histologically confirmed cases; Controls: no history of breast cancer	145	240	Non-smokers	1.00	Matched for age and residence
							Current or ex-smokers	3.33(1.63–6.80)	Adjusted for family history of breast cancer, education, menopausal status, age at menarche, parity and age at primiparity
					65 premenopausal	96 premenopausal	Non-smokers	1.00	
							Current or ex-smokers	1.89(0.72–4.99)	
					54 postmenopausal	89 postmenopausal	Non-smokers	1.00	
							Current or ex-smokers	6.26(1.64–23.9)	
Tung et al.	1999	1990–1995	Hospital-based (Osaka Medical Center for Cancer and Cardiovascular disease)	Cases: histologically confirmed cases; Controls: patients without diagnosis of cancer	376	430	Non-smokers	1.00	Adjusted for age, age at menarche, age at first delivery, weight, height, drinking and education
							Ex-smokers	0.98(0.54–1.78)	
							Smokers	0.90(0.55–1.49)	
					190 premenopausal	119 premenopausal	Non-smokers	1.00	
							Ex-smokers	0.82(0.32–2.09)	
							Smokers	0.71(0.32–1.58)	
					186 postmenopausal	282 postmenopausal	Non-smokers	1.00	
							Ex-smokers	0.94(0.39–2.27)	
							Smokers	0.97(0.47–1.98)	