Table 3. Summary of cohort studies on cigarette smoking and liver cancer among Japanese

Reference	Study period	Study population					Magnitude of association
		Sex	Number of subjects	Age range	Event	Number of incident cases or deaths	
Kono et al. (8)	1965–1983	Men	5130	Not specified	Death	51	–
Akiba and Hirayama (9)	1966–1981	Men	122 261	⩾40	Death	652	↑↑
		Women	142 857	⩾40	Death	398	↑↑↑
Inaba et al. (10)	1973–1988	Men	270 (liver cirrhosis)	Not specified	Death	46	↑↑
Shibata et al. (11)	1958–1986	Men	639 (farming area)	40–69	Death	11	–
			677 (fishing area)	40–69	Death	22	↑↑
Kato et al. (12)	1987–1990	Men and women	1784 (cirrhosis and post-transfusion hepatitis)	⩾16	Incidence	122	–
Tsukuma et al. (13)	1987–1991	Men and women	917 (chronic liver disease)	40–69	Incidence	54	↑↑↑
Goodman et al. (14)	1980–1989	Men	36 133 (men and women)	Not specified	Incidence	156	↑↑↑
		Women		Not specified	Incidence	86	↑
Chiba et al. (15)	1977–1993	Men and women	412 (HCV-associated chronic liver disease)	40–72	Incidence	63	↑↑↑
Tanaka et al. (16)	1985–1995	Men and women	96 (liver cirrhosis)	40–69	Incidence	37	–
Mori et al. (17)	1992–1997	Men and women	3052	⩾30	Incidence	22	↑
Mizoue et al. (18)	1986–1996	Men	4050	⩾40	Death	59	↑↑
Ogimoto et al. (19)	1988–1999	Men	28 287	40–79	Death	186 (number by sex not described)	↑↑↑
		Women	37 241	40–79	Death		↑↑

HCV, hepatitis C virus; ↑↑↑, strongly positive; ↑↑, moderately positive; ↑, weakly positive; –, no association.

Table 4. Summary of case–control studies on cigarette smoking and liver cancer among Japanese

Reference	Study period	Study subjects				Magnitude of association
		Sex	Age range	Number of cases	Number of controls	
Oshima et al. (20)	1972–1980	Men	Not specified	19	38	↑↑
Tsukuma et al. (21)	1983–1987	Men and women	⩽74	229	266	–
Tanaka et al. (22)	1985–1989	Men and women	40–69	204	410	–
Fukuda et al. (23)	1986–1992	Men and women	40–69	368	485	↓
Murata et al. (24)	1984–1993	Men	Not specified	66	132	↓↓
Shibata et al. (25)	1992–1995	Men	40–69	115	115 hospital controls	–
					115 community controls	–
Mukaiya et al. (26)	1991–1993	Men	Not specified	104	104 (chronic liver disease)	↑↑↑
Takeshita et al. (27)	1993–1996	Men	Not specified	85	101	↑
Koide et al. (28)	1994	Men and women	46–79	84	84	↑↑↑
Matsuo et al. (29)	1995–2000	Men	40–75	177	177 hospital controls	–
					177 community controls	↑↑↑
		Women	40–75	45	149 hospital controls	–
					149 community controls	↑↑
Munaka et al. (30)	1997–1998	Men and women	34–92	78	138	–

↑↑↑, strongly positive; ↑↑, moderately positive; ↑, weakly positive; –, no association; ↓, weakly inverse; ↓↓, moderately inverse.

infections was not addressed in most studies. Since, in Japan, individuals with either or both infections may have more than 100 times higher risk than those without either (3,31), only a slight change in smoking habit among such infected individuals could result in a substantial distortion of associated RRs. Alcohol consumption, another potential confounder, was not adequately controlled in some studies. In addition, the lack of dose–response relationship in three-quarters of the cohort studies has made our conclusion more conservative.

As for the case–control studies, the data have been controversial. In some studies, the recruitment of hospital controls, which possibly included those with smoking-related diseases, may have biased the RRs towards unity. Confounding issues by hepatitis virus infection and alcohol drinking were the same as those in the cohort studies. The absence of dose–response relation in majority of the case–control studies appears very perplexing. Among cases, symptoms resulting from pre-existing liver disease or physicians' advice on their health can lead to lifestyle changes including a reduction in number of cigarettes smoked per day. This might be responsible for elevated risks among light to moderate smokers observed in most case–control studies. However, the situation was similar in the cohort studies where smoking habit many years before the development of liver cancer was evaluated. Some unknown biological implications might exist in these non-linear relations.

An interaction issue between hepatitis viruses and cigarette smoking (i.e. possible difference in risk increase due to smoking according to hepatitis virus infection) should also be considered. Since the great majority of patients with hepatocellular carcinoma in Japan is known to be chronically infected with HBV or HCV (2,3), the following question naturally arises: 'Does smoking increase the risk of hepatocellular carcinoma among people without either HBV or HCV infection?' This question has not fully been addressed, probably due to the difficulty in conducting epidemiologic studies on this subject and its low practical implication in the prevention of liver cancer. It seems biologically implausible that cigarette smoking, without any hepatitis virus infection or heavy alcohol consumption, causes chronic liver disease, thereby playing a major role in hepatocarcinogenesis. On the other hand, the evaluation of the risk for smoking among people infected with HBV or HCV will be easier to be performed and will provide more practical information. It is noteworthy that, based on such evaluations, a limited number of cohort or case–control studies demonstrated clear dose–response relationships between smoking and liver cancer risk (13,15,20).

Finally, the authors consider that it will be problematic to perform a meta-analysis to obtain a summary estimate for the overall magnitude of association, since such an estimate may not be applicable to general populations of the Japanese due to the above interaction issue. Therefore, the planned meta-analysis was not conducted in this particular evaluation. In addition, the authors cannot exclude the possibility of publication bias and missing relevant epidemiologic studies, although they have long been knowledgeable about the situation of such studies in Japan.

EVALUATION OF THE EVIDENCE ON CIGARETTE SMOKING AND LIVER CANCER RISK AMONG JAPANESE

From these results and based on assumed biological plausibility as previously done by the International Agency for Research on Cancer (5), we conclude that cigarette smoking 'probably' increases the risk of primary liver cancer among the Japanese. Potential confounding by hepatitis virus infection and virus–smoking interactions need to be addressed in future studies.

Acknowledgments

The authors gratefully acknowledge the assistance of Ms Izumi Suenega and Mr Tomohiro Shintani in this review. This work was supported by the Third Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare, Japan.

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Jpn J Clin Oncol 2006;36(6)387–394
doi:10.1093/jjco/hyl031

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

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Received January 30, 2006; accepted March 7, 2006; published online June 9, 2006

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

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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		Study period	Study population	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
Author	Year		Number of subjects for analysis								
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		Study time	Study subjects	Definition	Number of cases	Number of controls	Category (smoking)	Odds ratio (95%CI)	*p* for trend	Confounding variables considered
Author	year		Type and source							
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)	

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

References			Study period	Study population					Magnitude of association
Author	Year	(Ref. no.)		Sex	Number of subjects	Age	Event	Number of incident cases or deaths	
Hirayama T	1990	(5)	1966–1982	Women	142 857	40 years or over	Mortality	241	—
Goodman MT	1997	(6)	1979–1987	Women	22 200	NA	Incidence	161	—
Hanaoka T	2005	(7)	1990–1999	Women	21 805	40–59	Incidence	180	↑↑

NA, not available.
*↑↑↑or ↓↓↓, strong; ↑↑or↓↓, moderate; ↑or↓, weak; —, no association (see text for more detailed definition).

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

References			Study period	Study subjects				Magnitude of association*
Author	Year	(Ref. no.)		Sex	Age	Number of cases	Number of controls	
Hirohata T	1985	(8)	Not specified	Women	NA	212	424	—
Kato I	1989	(9)	1980–1986	Women	20 year or over	1740	8920	—
Kato I	1992	(10)	1990–1991	Women	20 year or over	908	908	—
Wakai K	1994	(11)	1990–1991	Women	20 year or over	300	900	↑↑
						168 premenopausal	472 premenopausal	—
						127 postmenopausal	390 postmenopausal	↑↑↑
Hirose K	1995	(12)	1988–1992	Women	18 year or over	607 premenopausal	15 084 premenopausal	↑
						445 postmenopausal	6215 postmenopausal	—
Hu YH	1997	(13)	1989–1993	Women	25 year or over	157	369	↑↑↑
Uegi M	1998	(14)	1990–1997	Women	26–69 year or over	145	240	↑↑↑
						65 premenopausal	96 premenopausal	↑↑
						54 postmenopausal	89 postmenopausal	↑↑↑
Tung HT	1999	(15)	1990–1995	Women	Cases (mean = 51.6)	376	430	—
					Controls (mean = 54.5)	190 premenopausal	119 premenopausal	—
						186 postmenopausal	282 postmenopausal	—

NA, not available.
*↑↑↑or ↓↓↓, strong; ↑↑or↓↓, moderate; ↑or↓, weak; —, no association (see text for more detailed definition).

among women who smoke. Concerning these genotypes, Japanese appear to have higher frequency for GSTT1-null and CYP1A1*2A but not for the others compared with Caucasians (36–38). Confounding by other unmeasured factors, such as diet including phytoestrogen intake, cannot be excluded.

Integration of evidence based on case-control studies is compromised because of limitations in participants' memory of past exposure history and selection biases introduced in the recruitment of cases and controls. There was a tendency that positive association was reported in the case-control studies with small sample size. In addition, we cannot exclude the effect of publication bias. The number of cohort studies is insufficient to draw a definite conclusion.

EVALUATION OF THE EVIDENCE ON TOBACCO SMOKING AND BREAST CANCER RISK IN JAPANESE

From these results and assumed biological plausibility, we conclude that tobacco smoking possibly increases the risk of breast cancer in the Japanese population.

Acknowledgments

This work was supported by the Third Term Comprehensive 10 year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare, Japan.

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Jpn J Clin Oncol 2006;36(5)309–324
doi:10.1093/jjco/hyl025

Tobacco Smoking and Lung Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiological Evidence Among the Japanese Population

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Received December 19, 2005; accepted March 12, 2006; published online May 30, 2006

Background: Although tobacco smoking is the best established risk factor for lung cancer, the association is not as strong among Japanese as among Western populations. It would be of value, therefore, to quantify that association in Japan based on a systematic review of epidemiological evidence for the primary prevention of lung cancer.
Methods: Original data were obtained from MEDLINE searches using PubMed, supplemented with manual searches. The evaluation of associations was based on the strength of evidence and the magnitude of the association, together with biological plausibility as previously evaluated by the International Agency for Research on Cancer. A meta-analysis was also conducted to estimate the summary measure of those associations.
Results: A total of 8 cohort studies and 14 case–control studies were identified, almost all of which consistently showed a strong association of current smoking with the risk of lung cancer. The summary relative risk for current smokers versus never smokers was estimated as 4.39 (95% confidence interval 3.92–4.92) for men and 2.79 (95% confidence interval 2.44–3.20) for women. Cohort studies and case–control studies gave reasonably consistent summary measures. The summary relative risks were 11.7 and 2.30 for squamous cell carcinoma and adenocarcinoma, respectively, in men, and were 11.3 and 1.37 correspondingly in women.
Conclusion: There is convincing evidence that tobacco smoking strongly increases the risk of lung cancer in the Japanese population, with the relative risk for current smokers compared with never smokers measuring around 4.4 for men and 2.8 for women.

Key words: systematic review – epidemiology – smoking – lung neoplasms – Japanese

INTRODUCTION

Although tobacco smoking is the best established risk factor for lung cancer, the association between smoking and that risk is not as strong among Japanese as among Western populations. The relative risk (RR) of current smokers is much smaller in Japan than in Western countries, where the RR reaches more than 10 in men (1). This may mean that the epidemiological information on smoking and lung cancer from Western countries is not directly applicable to Japanese.

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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	5	1.00		Age and observation period
						Past	5	1.73 (0.09–11.3)		
						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)	