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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.

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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.

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		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
Author	Year										
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.

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

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