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

References		Study period	Study population					Strength of association[a]
Author	Year		Sex	Number of subjects	Ranged age	Event	Number of incident cases or deaths	
Goodman et al. (14)	1997	1979–87	Women	22 200	Not specified	Incidence	161	—
Iwasaki et al. (16)	2007	1990–2002	Women	55 537	40–69	Incidence	441	—
Kawai et al. (18)	2010	1990–2003	Women	24 064	40–64	Incidence	285	—

[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓ weak; -, no association (see text for more detailed definition).

Table 4. Summary of the association between breastfeeding and breast cancer risk, case–control study

References		Study period	Study subjects				Strength of association[a]
Author	Year		Sex	Age range	Number of cases	Number of controls	
Yoo et al. (8)	1992	1988–89	Women	Not specified	521	521	↓↓
Wakai et al. (11)	1994	1990–91	Women	20 year or over	300	900	–
Hu et al. (12)	1997	1989–93	Women	25 year or over	157	369	↓
Minami et al. (13)	1997	1987–91	Women	30 year or over	204	810	↓↓
Saeki et al. (17)	2008	2005	Women	45–69 years	3434	2427	↓

[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; –, no association (see text for more detailed definition).

have never breastfed may be more likely to be those who attempted to breastfeed but were unsuccessful. Ability to successfully breastfeed may have contributed to the potential protective effects of breastfeeding. However, there is no consistent evidence for the association between experience of insufficient milk supply and the risk of breast cancer (20). Possible confounders other than the number of births and age at first birth should also be considered. Minami et al. (19) reported that Japanese women with a high educational level or with a history of breast cancer in mother were less likely to choose breastfeeding only. Inadequate control for confounding may have resulted in an overestimation of the true effect of breastfeeding. The observed risk reduction appeared to be somewhat stronger in case–control studies than that in cohort studies. This trend would be due to publication bias in case–control studies, in that more strongly 'positive' study finding may have been more likely to be accepted for publication. We cannot also deny the possibility of selection bias or recall bias in case–control studies. However, small number of studies and the lack of information on the risk associated with longer duration of breastfeeding in the cohort studies preclude us to compare the results between the cohort and the case–control studies. Besides cumulative duration of breastfeeding, characterization of breastfeeding such as initiation of breastfeeding, number of children breastfed, quantification of mixed feeding and reasons for cessation for breastfeeding would be expected for future studies.

Possible mechanisms that contributed to the protective effects of breastfeeding include reduced systemic estrogen and progesterone levels, increased prolactin, excretion of estrogens and carcinogens out of the breast ducts, terminal differentiation of breast epithelial cells brought on by breastfeeding and delay in return of ovulation (21). It is biologically plausible that breastfeeding is related to breast cancer.

EVALUATION OF EVIDENCE ON BREASTFEEDING AND BREAST CANCER RISK IN JAPANESE

From these results, we conclude that breastfeeding possibly decreases the risk of breast cancer among Japanese population. On the basis of epidemiologic studies in the world and assumed biological plausibility, some evaluations conclude that breastfeeding decreases the risk of breast cancer. This evaluation is not contradictive with their conclusions. Even in the absence of strong evidence for protection against breast cancer in this review, breastfeeding requires continued promotion and support because of its other known benefits to the mother and the child.

Acknowledgements

The authors gratefully acknowledge the assistance of Ms. Izumi Suenaga.

Funding

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

Conflict of interest statement

None declared.

References

1. Newcomb PA. Lactation and breast cancer risk. *J Mammary Gland Biol Neoplasia* 1997;2:311–8.
2. Lipworth L, Bailey LR, Trichopoulos D. History of breast-feeding in relation to breast cancer risk: a review of the epidemiologic literature. *J Natl Cancer Inst* 2000;92:302–12.
3. Yang L, Jacobsen KH. A systematic review of the association between breastfeeding and breast cancer. *J Womens Health* 2008;17:1635–45.
4. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet* 2002;360:187–95.
5. World Cancer Research Fund, American Institute for Cancer Research. Lactation. In: *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington: American Institute for Cancer Research, 2007; 239–42.
6. Inoue M, Tsuji I, Wakai K, Nagata C, Mizoue T, Tanaka K, et al. Evaluation based on systematic review of epidemiological evidence among Japanese populations: tobacco smoking and total cancer risk. *Jpn J Clin Oncol* 2005;35:404–11.
7. World Health Organization. WHO Technical Reports Series 916. Diet, Nutrition, the Prevention of Chronic Disease. Report of a Joint WHO/FAO Expert Consultation. Geneva: WHO; 2003.
8. Yoo KY, Tajima K, Kuroishi T, Hirose K, Yoshida M, Miura S, et al. Independent protective effect of lactation against breast cancer: a case-control study in Japan. *Am J Epidemiol* 1992;135:726–33.
9. Land CE, Hayakawa N, Machado SG, Yamada Y, Pike MC, Akiba S, et al. A case-control interview study of breast cancer among Japanese A-bomb survivors. I main effects. *Cancer Causes Control* 1994;5:157–65.
10. Land CE, Hayakawa N, Machado SG, Yamada Y, Pike MC, Akiba S, et al. A case-control interview study of breast cancer among Japanese A-bomb survivors. II. Interactions with radiation dose. *Cancer Causes Control* 1994;5:167–76.
11. Wakai K, Ohno Y, Watanabe S, Sakamoto G, Kasumi F, Suzuki S, et al. Risk factors for breast cancer among Japanese women in Tokyo: a case-control study. *J Epidemiol* 1994;4:65–71.
12. Yao-Hua H, Nagata C, Shimizu H, Kaneda N, Kashiki Y. Association of body mass index, physical activity, and reproductive histories with breast cancer: a case-control study in Gifu, Japan. *Breast Cancer Res Treat* 1997;43:65–72.
13. Minami Y, Ohuchi N, Fukao A, Hisamichi S. Risk factors for breast cancer: a case-control study of screen-detected breast cancer in Miyagi Prefecture, Japan. *Breast Cancer Res Treat* 1997;44:225–3.
14. Goodman MT, Cologne JB, Moriwaki H, Vaeth M, Mabuchi K. Risk factors for primary breast cancer in Japan: 8-year follow-up of atomic bomb survivors. *Prev Med* 1997;26:144–533.
15. Hirose K, Tajima K, Hamajima N, Kuroishi T, Kuzuya K, Miura S, et al. Comparative case-referent study of risk factors among hormone-related female cancers in Japan. *Jpn J Cancer Res* 1999;90:255–61.
16. Iwasaki M, Otani T, Inoue M, Sasazuki S, Tsugane S. Role and impact of menstrual and reproductive factors on breast cancer risk in Japan. *Eur J Cancer Prev* 2007;16:116–23.
17. Saeki T, Sano M, Komoike Y, Sonoo H, Honjyo H, Ochiai K, et al. No increase of breast cancer incidence in Japanese women who received hormone replacement therapy: overview of a case-control study of breast cancer risk in Japan. *Int J Clin Oncol* 2008;13:8–11.
18. Kawai M, Minani Y, Kuriyama S, Kakizaki M, Kakugawa Y, Nishino Y, et al. Reproductive factors, exogenous female hormone use and breast cancer risk in Japanese: the Miyagi cohort study. *Cancer Causes Control* 2010;21:135–45.
19. Minami Y, Ohuchi N, Fukao A, Hisamichi S. Determinants of infant feeding method in relation to risk factors for breast cancer. *Prev Med* 2000;30:363–70.
20. Cohen JM, Hutcheon JA, Julien SG, Tremblay ML, Fuhrer R. Insufficient milk supply and breast cancer risk: a systematic review. *PLos ONE* 2009;4:e8237.
21. Eden JA. Breast cancer, stem cells and sex hormones, Part 2: the impact of the reproductive years and pregnancy. *Maturitas* 2010;67:215–8.

Appendix

Research group members: Shoichiro Tsugane (principal investigator), Manami Inoue, Shizuka Sasazuki, Motoki Iwasaki, Tetsuya Otani (until 2006), Norie Sawada (since 2007), Taichi Shimazu (since2007) (National Cancer Center, Tokyo); Ichiro Tsuji (since 2004), Yoshitaka Tsubono (in 2003) (Tohoku University, Sendai); Yoshikazu Nishino (until 2006) (Miyagi Cancer Research Institute, Natori, Miyagi); Akiko Tamakoshi (since 2010) (Aichi medical University, Aichi); Keitaro Matsuo (until 2010), Hidemi Ito (since 2010) (Aichi Cancer Center, Nagoya); Kenji Wakai (Nagoya University, Nagoya); Chisato Nagata (Gifu University, Gifu); Tetsuya Mizoue (National Center for Global Health and Medicine, Tokyo); Keitaro Tanaka (Saga University, Saga).

Japanese Journal of Clinical Oncology Advance Access published February 27, 2012

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2012
doi:10.1093/jjco/hys009

Public Health Report

Green Tea Consumption and Gastric Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence Among the Japanese Population

Shizuka Sasazuki[1,*], Akiko Tamakoshi[2], Keitaro Matsuo[3], Hidemi Ito[3], Kenji Wakai[4], Chisato Nagata[5], Tetsuya Mizoue[6], Keitaro Tanaka[7], Ichiro Tsuji[8], Manami Inoue[1] and Shoichiro Tsugane[1] for the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan

[1]Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, [2]Department of Public Health, Aichi Medical University School of Medicine, Nagakute, [3]Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, [4]Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Nagoya, [5]Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu, [6]Department of Epidemiology and International Health, Research Institute, International Medical Center of Japan, Tokyo, [7]Department of Preventive Medicine, Saga Medical School, Faculty of Medicine, Saga University, Saga and [8]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

*For reprints and all correspondence: Shizuka Sasazuki, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji Chuo-ku, Tokyo 104-0045 Japan. E-mail: ssasazuk@ncc.go.jp

Received October 19, 2011; accepted January 24, 2012

Objective: Numerous *in vitro* and animal studies have shown that green tea has a protective effect against cancer. However, results from epidemiologic studies are conflicting. We evaluated the association between green tea consumption and risk for gastric cancer risk among the Japanese population based on a systematic review of epidemiologic evidence.

Methods: Original data were obtained from MEDLINE searches using PubMed or from searches of the *Ichushi* database, complemented with manual searches. Evaluation of associations was based on the strength of evidence and the magnitude of association, together with biologic plausibility.

Results: Eight cohort studies and three case–control studies were identified. Overall, we found no preventive effect on gastric cancer for green tea intake in cohort studies. However, a small, consistent risk reduction limited to women was observed, which was confirmed by pooling data of six cohort studies (hazard ratio = 0.79, 95% confidence interval 0.65–0.96 with $\geq$5 cups/day of green tea intake). Case–control studies consistently showed a weak inverse association between green tea intake and gastric cancer risk.

Conclusions: We conclude that green tea possibly decreases the risk of gastric cancer in women. However, epidemiologic evidence is still insufficient to demonstrate any association in men.

Key words: systematic review – epidemiology – green tea – gastric cancer – Japanese

BACKGROUND

Although the age-standardized mortality rate has been continuously declining, gastric cancer is still the second leading cause of cancer deaths among men and women in Japan (1). In addition to *Helicobacter pylori* infection or cigarette smoking, dietary factors are suggested to be associated with gastric carcinogenesis (2).

Numerous *in vitro* and animal studies have shown that green tea has a protective effect against cancer (3). These experimental studies have suggested that green tea polyphenols might have a protective effect against gastric cancer through its apoptosis-inducing, antimutagenic and antioxidant activities. In 1997, a review of the World Cancer Research Fund, based on the results of case–control studies and several animal models that showed a protective effect of green tea, stated that 'green tea possibly reduce the risk of stomach cancer' (4). Since then, results from cohort studies generally have not supported the findings from case–control studies, and the more recent 2007 report concluded that 'the evidence was so limited that no firm conclusion can be made' (5).

In Japan, green tea is one of the most commonly consumed beverages, and therefore, the effect of green tea on the risk for gastric cancer may be of particular concern. We reviewed epidemiologic studies of green tea consumption and gastric cancer risk among Japanese. This work was conducted as a systematic review of epidemiologic studies on lifestyle factors and cancer based on previous publications targeting Japanese (6).

METHODS

Research Review

Details of the evaluation method have been described previously (6). Briefly, original data for this review were identified through searches of the MEDLINE (PubMed) and *Ichushi (Japana Centra Revuo Medicina)* databases, complemented by manual searches of references from relevant articles where necessary. All epidemiologic studies on the association between green tea intake and gastric cancer incidence/mortality among the Japanese from 1950 (or 1983 for the *Ichushi* database) to June 2011 were identified using the search terms 'green tea', 'tea', 'gastric cancer', 'stomach cancer', 'cancer', 'cohort study', 'case-control study', 'Japan' and 'Japanese' as key words. In addition, we manually searched through references from relevant articles where necessary. Papers written in either English or Japanese were reviewed, and only studies on Japanese populations living in Japan were included. In the case of multiple publications of analyses of the same or overlapping data sets, only data from the largest or the most recent studies were included. The individual results were summarized in the tables separately as cohort or case–control studies. Pooled data of Japanese cohort studies, including some of the individual studies already listed, were also available through the review process. To better understand the results from individual studies and finally evaluate the evidence for green tea intake and gastric cancer risk in Japanese, findings from recent pooled analyses were also listed and considered in this report.

Evaluation of Strength of Association Between Green Tea Intake and Gastric Cancer Risk

The evaluation was made based on the magnitude of association and the strength of evidence. First, the former was assessed by classifying the relative risk (RR) in each study into the following four categories, while considering statistical significance (SS) or no statistical significance (NS), as strong (symbol $\downarrow\downarrow\downarrow$ or $\uparrow\uparrow\uparrow$), <0.5 or >2.0 (SS); moderate (symbol $\downarrow\downarrow$ or $\uparrow\uparrow$), either (i) <0.5 or >2.0 (NS), (ii) >1.5–2 (SS) or (iii) 0.5 to <0.67 (SS); weak (symbol $\downarrow$ or $\uparrow$), either (i) >1.5–2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association (symbol –), 0.67–1.5 (NS). In cases where the frequency or amount of green tea intake had been separated into levels in a study, we used the RR derived from comparing the highest intake with the lowest. To consider the intermediate categories of intake, however, the *P* value for the trend was also considered when judging the statistical significance. After this process, the strength of evidence was evaluated in a manner similar to that used in the WHO/FAO Expert Consultation Report, where evidence was classified as convincing, probable, possible and insufficient (7). We assumed that biologic plausibility was based on evidence in experimental models, human studies and other relevant data.

MAIN FEATURES AND COMMENTS

Through the review process, we identified eight cohort studies (8–15), one pooled analysis of six cohort studies (16) (Table 1) and three case–control studies (17–19) (Table 2). Among cohort studies, the events followed were death in five studies (8,10,12,14,15) and incidence in the other three studies (9,11,13). Five studies showed the results for men and women separately (9,10–14), whereas three studies showed combined results only (8,13,15). The pooled analysis included four cohorts (9,10 and two cohorts in 11) listed in Table 1 and two other cohorts (20,21). For all case–control studies, the results were shown for men and women combined.

The summary of the magnitudes of association for the cohort study and the case–control study is presented in Tables 3 and 4, respectively. As shown in Table 3, among eight cohort studies, one study showed a weak positive association between green tea intake and gastric cancer risk in men (9). Women in the study and all other studies showed no association at all. When the anatomic subsite was considered, one study observed a moderate inverse association for distal cancer in women (11). On the other hand, case–

Table 1. Gastric cancer risk and consumption of green tea in cohort studies of Japanese populations

References	Study period	Study population				Category	No. among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
Author		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths						
Nakachi et al. (8)	1986–99	8552	Population-based Saitama Prefecture	Death	140	Green tea, cups/day				Sex and lifestyle factors	
						≤3		1.0			
						≥10		0.69 (0.23–1.88)			
Tsubono et al. (9)	1984–92	26 311	Population-based Miyagi Prefecture	Incidence	419	Green tea, cups/day				Age, sex, types of health insurance, history of peptic ulcer, smoking status, alcohol consumption, daily consumption of rice, black tea, coffee, meat, green or yellow vegetables, pickled vegetables, other vegetables, fruits and bean-paste soup	
		11 902 men			296 men	Total					
		14 409 women			123 women	<1	66	1.0			
						1–2	68	1.1 (0.8–1.6)			
						3–4	79	1.0 (0.7–1.4)			
						≥5	206	1.2 (0.9–1.6)	0.13		
						Men					
						<1	41	1.0			
						1–2	49	1.3 (0.8–1.9)			
						3–4	55	1.2 (0.8–1.8)			
						≥5	151	1.5 (1.0–2.1)	0.03		
						Women					
						<1	25	1.0			
						1–2	19	0.8 (0.5–1.5)			
						3–4	24	0.7 (0.4–1.3)			
						≥5	55	0.8 (0.5–1.3)	0.46		
Hoshiyama et al. (10)	Mean 8 years	72 851	Population-based 45 areas of Japan	Death	359	Green tea, cups/day				Age, smoking status, history of peptic ulcer, family history of stomach cancer, consumption of rice, miso soup, green– yellow vegetables, white vegetables, fruits and preference for salty foods	
		30 370 men			240 men	Men					
		42 481 women			119 women	<1	24	1.0			
						1–2	51	1.6 (0.9–2.9)			
						3–4	51	1.1 (0.6–1.9)			
						5–9	76	1.1 (0.6–1.9)			
						≥10	38	1.0 (0.5–2.0)	0.634		
						Women					
						<1	20	1.0			
						1–2	18	1.1 (0.5–2.5)			
						3–4	40	1.0 (0.5–2.1)			
						5–9	32	0.8 (0.4–1.6)			
						≥10	9	0.7 (0.3–2.0)	0.476		

Continued

Table 1. *Continued*

References	Study period	Study population				Category	No. among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
Author		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths						
Sasazuki et al. (11)	1990–2001	72,943	Population-based	Incidence	892	Green tea, cups/day				Age, area, cigarette smoking, consumption of fruits, green or yellow vegetables, fishgut, miso soup, black tea and coffee	
		34,832 men			665 men	Men					
		38,111 women			227 women	All sites					
						<1		1.0			
						1–2		0.95 (0.72–1.22)			
						3–4		0.84 (0.65–1.08)			
						≥5		0.98 (0.77–1.25)	0.65		
						Upper-third including cardia					
						<1		1.0			
						1–2		1.06 (0.51–2.18)			
						3–4		0.73 (0.34–1.57)			
						≥5		1.17 (0.60–2.30)	0.75		
						Distal					
						<1		1.0			
						1–2		0.88 (0.64–1.20)			
						3–4		0.79 (0.59–1.07)			
						≥5		0.92 (0.69–1.22)	0.37		
						Women					
						All sites					
						<1		1.0			
						1–2		0.85 (0.53–1.38)			
						3–4		1.04 (0.68–1.58)			
						≥5		0.67 (0.43–1.04)	0.08		
						Upper-third including cardia					
						<1		1.0			
						1–2					
						3–4		0.89 (0.34–2.33)			
						≥5			0.81		
						Distal					
						<1		1.0			
						1–2		0.88 (0.52–1.49)			
						3–4		1.00 (0.63–1.59)			
						≥5		0.51 (0.30–0.86)	0.01		

Khan et al. (12)	1984–2002	3158	Population-based Hokkaido	Death	51	Men				Age, smoking, health status, health education, health screening
		1524 men			36 men	Green tea ≤ several times/month		1.0		
		1634 women			15 women	Green tea ≥ several times/week		1.1 (0.4–2.5)		
						Women				
						Green tea ≤ several times/month		1.0		
						Green tea ≥ several times/week		0.7 (0.2–2.9)		
Sauvaget et al. (13)	1980–99	38 576	Atomic-bomb survivors: Hiroshima, Nagasaki	Incidence	1270	Green tea, cups/day				Sex, sex-specific age, city, radiation dose, sex-specific smoking habits and education level
		14 885 men				<2	242	1.0		
		23 691 women				2–4	680	1.03 (0.89–1.19)		
		34–98 years old				≥5	348	1.06 (0.89–1.25)	>0.50	
Kuriyama et al. (14)	All-cause	40 530	Population-based	Death	193	Green tea, cups/day				Age, sex, job status, years of education, BMI, sports or exercise, walking duration, history of HT, DM, GU, smoking, alcohol, total energy, rice, miso soup, soy bean product, total meat, total fish, dairy products, total fruits, total vegetables, oolong tea, black tea, and coffee
	1995–2005 (11 years)	19 060 men				<1	44	1.0		
		21 470 women				1–2	44	1.33 (0.86–2.04)		
	Cause-specific					3–4	38	1.00 (0.64–1.58)		
	1995–2001 (7 years)					5≤	67	1.17 (0.78–1.76)	0.72	
					138 men	<1	32	1.0		
						1–2	30	1.29 (0.78–2.16)		
						3–4	30	1.19 (0.71–2.00)		
						≥5	46	1.20 (0.74–1.95)	0.55	
					55 women	<1	12	1.0		
						1–2	14	1.32 (0.59–2.94)		
						3–4	8	0.64 (0.26–1.63)		
						≥5	21	1.08 (0.50–2.33)	0.84	
Suzuki et al. (15)	1999–2006	12 251	Population randomly chosen from all 74 municipalities in Shizuoka Prefecture	Death	68	Green tea, cups/day				Age, sex, smoking, alcohol, BMI, and physical activity
		6231 men				<1	2	1.0	Test for trend: HR = 1.04 (0.95–1.13)	
		6020 women				1–3	14	0.49 (0.11–2.28)		
		65–84y old				4–6	32	0.78 (0.19–3.30)		
						≥7	20	0.81 (0.18–3.54)		

Continued

Table 1. *Continued*

References	Study period	Study population				Category	No. among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
Author		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths						
Pooled analysis of 6 cohort studies including those listed above (9,10, cohort I of 11, cohort II of 11) or mentioned in the text (20 and 21)											
Inoue et al. (16)	1985–2004	219 080	Population-based	Incidence	3577	Green tea, cups/day					
		100 479 men			2495 men	Men				Age, area (for three cohorts only), smoking, alcohol drinking, rice, soy bean paste soup, coffee, pickled vegetables, and green-yellow vegetables intake	
		118 601 women			1082 women	All sites					
						<1	420	1.0			
						1–2	452	0.97 (0.83–1.12)			
						3–4	610	0.93 (0.81–1.08)			
						≥5	1013	1.06 (0.86–1.30)	0.74		
						Proximal (upper third)					
						<1	38	1.0			
						1–2	41	1.10 (0.70–1.73)			
						3–4	42	0.79 (0.46–1.35)			
						≥5	96	1.43 (0.96–2.14)	0.08		
						Distal (lower two-thirds)					
						<1	185	1.0			
						1–2	185	0.91 (0.73–1.12)			
						3–4	249	0.95 (0.77–1.16)			
						≥5	328	0.96 (0.79–1.17)	0.86		
						Women					
						All sites					
						<1	215	1.0			
						1–2	174	0.90 (0.73–1.10)			
						3–4	303	0.92 (0.76–1.11)			
						≥5	390	0.79 (0.65–0.96)	0.04		
						Proximal (upper third)					
						<1	8	1.0			
						≥1	45	1.17 (0.52–2.60)	0.87		
						Distal (lower two thirds)					
						<1	83	1.0			
						1–2	64	0.80 (0.57–1.13)			
						3–4	117	0.96 (0.71–1.30)			
						≥5	106	0.70 (0.50–0.96)	0.04		

NS, not significant; BMI, body mass index; HT, hypertension; DM, diabetes mellitus; GU, gastric ulcer.

Table 2. Gastric cancer risk and consumption of green tea in case–control studies of Japanese populations

References	Study time	Study subjects				Category	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
Author		Type and source	Definition	No. of cases	No. of controls					
Tajima and Tominaga (17)	1981–83	Hospital-based (Aichi Cancer Center)	Cases:	93	186	Green tea, times/day			Matched for age (±5 years), sex, time of interviews (±6 months)	
			Histologically confirmed cases			≥4	0.64	NS		
			Controls:			≤3	1.0			
			Patients without stomach cancer							
Kono et al. (18)	1979–82	Hospital-based (Karatsu Stomach Institute)	Cases:	139	Hospital controls: 2574	vs. hospital controls				
			Newly diagnosed as having gastric cancer at the Institute	74 men		Green tea, cups/day				
				65 women	1171 men	None or 1–4	1.0		Age, sex	
					1403 women	5–9	1.1			
						≥10	0.6	NS		
			Hospital controls:		General controls;					
			Patients without gastric cancer		278	≤9	1.0		Age, sex, smoking, oranges, fruits	
					148 men	≥10	0.5 (0.3–1.1)			
			General population controls:		130 women					
			Random sampling from the computerized file of residents			vs. general controls			General population:	
						Green tea, cups/day			Matched (1:2) for	
						None or 1–4	1.0		Sex	
						5–9	1.2		Age	
						≥10	0.4*	NS		
						≤9	1.0		Smoking, oranges, fruits	
						≥10	0.3 (0.1–0.7)†			

Continued

Table 2. *Continued*

References	Study time	Study subjects			Category	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
Author		Type and source	Definition	No. of cases	No. of controls				
Inoue et al. (19)	1990–95	Hospital-based (Aichi Cancer Center)	Cases:	893	21 128	Green tea			
			Histologically diagnosed cases of gastric cancer at the Institute			Rarely	1.00	Coffee intake, black tea intake, gender, age, year and season at first hospital visit, habitual smoking, habitual alcohol drinking, regular physical exercise, fruit intake, rice intake, and beef intake	
						Occasional	1.00 (0.77–1.44)		
						Daily			
			Controls:			1–3 cups/day	0.96 (0.70–1.32)		
			Outpatients without cancer			4–6 cups/day	1.01 (0.74–1.39)		
						≥7 cups/day	0.69 (0.48–1.00)‡		

NS, not significant.
*$P < 0.05$.
†$P = 0.007$.
‡$P < 0.05$.

control studies consistently showed a weak negative association between intake of green tea and risk of gastric cancer (Table 4). Among them, when using the general population as a control setting, Kono et al. (18) observed a strong negative association between green tea intake and gastric cancer risk.

During the review process, we were aware of the difference in effect by sex. In all studies that presented the analysis for men and women separately, although not statistically significant, the point estimate of highest category of green tea intake for women was consistently lower than that for men; i.e. based on incidence data, compared with <1 cup/day, the RRs of drinking ≥5 cups/day for men and women were estimated as 1.5 and 0.8 (9) and 0.98 and 0.67 (11), respectively (Table 1). Based on mortality data, the corresponding values for men and women were estimated as 1.0 and 0.7 (<1 vs. ≥10 cups/day) (10), and 1.1 and 0.7 (less than several times per month vs. more than several times per week) (12), respectively (Table 1). These results suggest a small protective effect, if any, of green tea intake and development of gastric cancer for women. However, applying our definition of magnitudes of association, they slightly failed to reach the level of weak association (weak association for 0.5 to <0.67, not significant). The null association observed among men may, in part, reflect insufficient adjustment for confounding factors such as cigarette smoking. Likewise, differences in the effect of green tea by subsite may point to an inconsistent effect on gastric cancer overall (11). However, evidence for such specific issues is sparse, probably due to the relatively small number of gastric cancer cases occurring in the upper subsite among cohorts, particularly in women. Results from pooled analysis may lead to a better understanding of these unresolved issues.

In a pooled analysis of six cohort studies (9–11,13,20,21) involving total of 219 080 subjects and 3577 gastric cancer cases, the role of green tea intake and gastric cancer risk was analyzed for men and women separately, with consideration of smoking status, anatomic subsite and so on (16). As a result, a statistically significant, weakly decreased risk of gastric cancer with ≥5 cups/day of green tea intake among women was observed [hazard ratio (HR) = 0.79, 95% confidence interval (CI) 0.65–0.96], although no association was observed among men (Tables 1 and 3). When the anatomic subsite was considered among four cohort studies in which the data were routinely collected, the risk reduction among women was more prominent in the distal gastric region (HR = 0.70, range 0.50–0.96; *P* for trend = 0.04). Together with the results of the systematic review, this finding from the pooled analysis was also considered to finally evaluate the evidence for green tea intake and gastric cancer risk in Japanese.

A difference in the effect of green tea intake by sex has also been observed for cardiovascular disease (14,22,23). The exact reason for the difference is unknown but may be explained, in part, by residual confounding effects of

smoking, phytoestrogens in tea and so on. It was suggested in some studies (9,14), but not all (16), that cigarette smoking might modify the effect of green tea. Tsubono et al. (9) observed a trend toward a positive association between green tea consumption and the risk of gastric cancer in subjects currently smoking ≥20 cigarettes/day (P for trend = 0.06), but not in other groups (P for the interaction term = 0.17). A similar interaction was suggested among studies investigating green tea intake and risk for cardiovascular disease (14). Higher rates of smoking may mask the effect of green tea consumption in men. Tea flavonoids such as kaempferol have been shown to exhibit estrogenic activity *in vitro* (24). In addition, tea contains lignan polyphenols, such as secoisolaracinol, which are considered phytoestrogenic (25). The phytoestrogens in tea might also partly account for the stronger protective effect of green tea in women than in men (26,27), although an estrogen-related protective mechanism against gastric cancer, if any, warrants further investigation.

Several aspects need to be discussed in relation to interpreting the present findings. Although cigarette smoking, which is suggested to have an interactive effect with green tea, was adjusted in most studies, *H. pylori* infection, a Group 1 carcinogen recognized by the International Agency for Research on Cancer (IARC), was not considered in any study. Based on the same origin of cohort study (10), Hoshiyama et al. (28) investigated whether green tea has any association with gastric cancer risk with considering *H. pylori* infection in a nested case–control study design within 157 incidence cases and 285 controls. They found that green tea intake had no protective effect against gastric cancer even after controlling for *H. pylori* infection. A previous nested case–control study that investigated plasma tea polyphenols and risk for gastric cancer reported that the decreased risk of gastric cancer by intake of tea polyphenols observed among women in the study remained even after adjusting for *H. pylori* infection (29). Some researchers used an animal model to report the inhibition of *H. pylori* urease by green tea extract (30) and the bactericidal effect on *H. pylori* infection by green tea catechins (31). A long-term habit of drinking green tea might lead to the elimination of *H. pylori*; if this is true, *H. pylori* may act as an intermediate rather than a confounding factor in the relationship between green tea and gastric cancer.

Discrepancies were noted in the effects of green tea on gastric cancer risk between case–control studies and cohort studies. The discrepancies were quantitatively shown from a recent meta-analysis of green tea intake and gastric cancer risk based on 13 studies from Japan and China (32). Compared with the lowest level of green tea intake, the RR of gastric cancer for the highest level of green tea intake was 0.73 (95% CI 0.64–0.83) for case–control studies, whereas no association was observed for cohort studies (RR = 1.04, 95% CI 0.93–1.17). The discrepancy may be partially explained by recall or selection biases that are inevitable in case–control studies. For example, it is possible that individuals with gastric cancer reduce their green tea intake due to their gastric symptoms. In fact, it has been reported that among those with gastric cancer, black tea consumption was reduced even up to 2 years before their diagnosis was made (33). Therefore, the green tea intake for gastric cancer cases among case–control studies might be partly underreported. Another point is the variation of gastric cancer mortality rates across the country. The age-adjusted gastric cancer mortality rate under age 75 in 2009 in Japan was 11.8/100 000 and ranged from 6.3 (Okinawa prefecture) to 15.7 (Akita prefecture) (34). It is interesting that gastric cancer mortality rates in the two prefectures in the case–control studies are higher than the average level, whereas the situation for cohort studies is mixed. On the basis of wide variation in gastric cancer mortality rates by area, the approach such as pooled analysis might be important.

However, the null results in cohort studies also contradict the results of previous experimental studies that suggested the protective effect of tea polyphenols on gastric cancer using *in vivo* animal models and *in vitro* cancer cell lines (3). In most of the cohort studies where the validity of green tea intake was examined, a moderate validity was shown; the Spearman coefficient for the correlation between the green tea intake according to the questionnaire and the amounts consumed according to the food records ranged from 0.29 to 0.71 (9–11,13,14). However, in all epidemiologic studies investigating green tea intake and gastric cancer risk, green tea consumption was determined only in terms of self-reported frequency of drinking, and the size of the cup was not ascertained. Furthermore, the amount of tea polyphenols in one cup varies according to preparation, i.e. the type and amount of green tea leaves, the frequency of renewing a tea batch in the pot, the temperature of boiled water or time to brew the tea and so on. A number of studies have found that hot drinks have an effect on the risk for esophageal cancer (35). Yu et al. (36) also showed that boiling hot tea had a non-significant increased risk of causing gastric cancer (odds ratio = 1.18). The risk estimates for the cardia, pylori and antrum sites regarding boiling hot tea were 2.09, 0.56 and 0.82, respectively. Furthermore, the term 'green tea' might be ambiguous because some participants may include only 'sencha', which looks green, or others may also include 'bancha/houjicha/genmaicha', which is also a commonly consumed Japanese tea but looks brown. Sencha, one of the most popular green teas in Japan, contains higher levels of tannin, vitamin C and folate than bancha/houjicha/genmaicha (37). Inaccurate measurement of green tea consumption in epidemiologic studies necessarily attenuates the small effect of green tea. It is interesting that both studies using biomarkers of green tea intake showed a statistically significant association with gastric cancer. Sun et al. (38) reported that urinary (−)-epigallocatechin (EGC) showed a statistically significant inverse association with gastric cancer. In a case–control study nested within a cohort study (11), a high plasma level of EGC was associated with an increased risk of gastric cancer in men, whereas a high plasma level of

Table 3. Summary of associations between gastric cancer risk and consumption of green tea in cohort studies of Japanese populations

References			Study period	Study subjects				Strength of association
Author	Year	Ref. no.		Sex	No. of subjects	Age range	Event	No. of cases	
Nakachi et al.	2000	8	1986–99	Men and women	8552	40+	Death	140	–
Tsubono et al.	2001	9	1984–92	Men	11 902	40+	Incidence	296	↑
				Women	14 409			123	–
Hoshiyama et al.	2002	10	1988–97	Men	30 370	40–79	Death	240	–
				Women	42 481			119	–
Sasazuki et al.	2004	11	1990–2001	Men	34 832	40–59	Incidence	665	–
				Women	38 111			227	– (distal ↓↓)
Khan et al.	2004	12	1984–2002	Men	1524	40+	Death	36	–
				Women	1634			15	–
Sauvaget et al.	2005	13	1980–99	Men and women	38 576	34–98	Incidence	1270	–
Kuriyama et al.	2006	14	1995–2001	Men	19 060	40–79	Death	138	–
				Women	21 470			55	–
Suzuki et al.	2009	15	1999–2006	Men and women	12 251	65–84	Death	68	–
Pooled analysis of 6 cohort studies including those listed above (9,10, cohort I of 11, cohort II of 11) or mentioned in the text (20 and 21)									
Inoue et al.	2009	16	1985–2004	Men	100 479	40–103	Incidence	2495	–
				Women	118 601			1082	↓

Explanation for each symbol is as follows when statistical significance (SS) or no statistical significance (NS), strong (symbol ↓↓↓ or ↑↑↑), <0.5 or >2.0 (SS); moderate (symbol ↓↓ or ↑↑), either (i) <0.5 or >2.0 (NS), (ii) >1.5–2 (SS) or (iii) 0.5 to <0.67 (SS); weak (symbol ↓ or ↑), either (i) >1.5–2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association (symbol –), 0.67–1.5 (NS).

Table 4. Summary of associations between gastric cancer risk and consumption of green tea in case–control studies of Japanese populations

References			Study period	Study subjects				Strength of association
Author	Year	Ref. no.		Sex	Age range	No. of cases	No. of controls	
Tajima and Tominaga	1985	17	1981–83	Men and women	40–70	93	186	↓
Kono et al.	1988	18	1979–82	Men and women	20–75	139	Hospital 2547	↓
							General population 278	↓↓↓
Inoue et al.	1998	19	1990–95	Men and women	40+	893	21 128	↓

Explanation for each symbol is as follows when statistical significance (SS) or no statistical significance (NS), strong (symbol ↓↓↓ or ↑↑↑), <0.5 or >2.0 (SS); moderate (symbol ↓↓ or ↑↑), either (i) <0.5 or >2.0 (NS), (ii) >1.5–2 (SS) or (iii) 0.5 to <0.67 (SS); weak (symbol ↓ or ↑), either (i) >1.5–2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association (symbol –), 0.67–1.5 (NS).

(−)-epicatechin-3-gallate was associated with a statistically significant decreased risk of gastric cancer in women (29).

In conclusion, we found no preventive effect on gastric cancer for green tea intake in cohort studies, which have fewer biases and are more persuasive than case–control studies, where risk reduction was shown. However, a small, consistent risk reduction limited to women was observed, which was confirmed by pooling data from six cohort studies.

EVALUATION OF EVIDENCE ON GREEN TEA CONSUMPTION AND GASTRIC CANCER RISK IN JAPANESE

From the results of the systematic review and pooled analysis of green tea intake and gastric cancer risk and on the basis of assumed biologic plausibility, we conclude that green tea possibly decreases the risk of gastric cancer in women. However, epidemiologic evidence is still insufficient to demonstrate any association in men.

Acknowledgements

The authors gratefully acknowledge the assistance of Ms Izumi Suenaga in this report.

Funding

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

Conflict of interest statement

None declared.

References

1. Center for Cancer Control and Information Services [NCC website]. Trend in age-standardized cancer mortality rate, 1958 through 2009. http://ganjoho.jp/pro/statistics/en/gdb_trend.html?1%1 [cited 3 August 2011].
2. Kelley JR, Duggan JM. Gastric cancer epidemiology and risk factors. *J Clin Epidemiol* 2003;56:1–9.
3. Yang CS, Lee MJ, Chen L, Yang GY. Polyphenols as inhibitors of carcinogenesis. *Environ Health Perspect* 1997;105(Suppl 4):971–6.
4. World Cancer Research Fund/AICR. *Food, Nutrition and the Prevention of Cancer: A Global Perspective*. Washington, DC: American Institute for Cancer Research 1997.
5. World Cancer Research Fund/AICR. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: Global Perspective*. Washington, DC: American Institute for Cancer Research 2007.
6. Inoue M, Tsuji I, Wakai K, Nagata C, Mizoue T, Tanaka K, et al., Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Evaluation based on systematic review of epidemiological evidence among Japanese populations: tobacco smoking and total cancer risk. *Jpn J Clin Oncol* 2005;35:404–11.
7. World Health Organization. *WHO Technical Reports Series 916. Diet, Nutrition and Prevention of Chronic Diseases: Report of a Joint WHO/FAO Expert Consultation*. Geneva, Switzerland: WHO 2003.
8. Nakachi K, Matsuyama S, Miyake S, Suganuma M, Imai K. Preventive effects of drinking green tea on cancer and cardiovascular disease: epidemiological evidence for multiple targeting prevention. *Biofactors* 2000;13:49–54.
9. Tsubono Y, Nishino Y, Komatsu S, Hsieh CC, Kanemura S, Tsuji I, et al. Green tea and the risk of gastric cancer in Japan. *N Engl J Med* 2001;344:632–6.
10. Hoshiyama Y, Kawaguchi T, Miura Y, Mizoue T, Tokui N, Yatsuya H, et al. A prospective study of stomach cancer death in relation to green tea consumption in Japan. *Br J Cancer* 2002;87:309–13.
11. Sasazuki S, Inoue M, Hanaoka T, Yamamoto S, Sobue T, Tsugane S. Green tea consumption and subsequent risk of gastric cancer by subsite: the JPHC Study. *Cancer Causes Control* 2004;15:483–91.
12. Khan MM, Goto R, Kobayashi K, Suzumura S, Nagata Y, Sonoda T, et al. Dietary habits and cancer mortality among middle aged and older Japanese living in Hokkaido, Japan by cancer site and sex. *Asian Pac J Cancer Prev* 2004;5:58–65.
13. Sauvaget C, Lagarde F, Nagano J, Soda M, Koyama K, Kodama K. Lifestyle factors, radiation and gastric cancer in atomic-bomb survivors (Japan). *Cancer Causes Control* 2005;16:773–80.
14. Kuriyama S, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, et al. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. *J Am Med Assoc* 2006;296:1255–65.
15. Suzuki E, Yorifuji T, Takao S, Komatsu H, Sugiyama M, Ohta T, et al. Green tea consumption and mortality among Japanese elderly people: the prospective Shizuoka elderly cohort. *Ann Epidemiol* 2009;19:732–9.
16. Inoue M, Sasazuki S, Wakai K, Suzuki T, Matsuo K, Shimazu T, et al., Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Green tea consumption and gastric cancer in Japanese: a pooled analysis of six cohort studies. *Gut* 2009;58:1323–32.
17. Tajima K, Tominaga S. Dietary habits and gastro-intestinal cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. *Jpn J Cancer Res* 1985;76:705–16.
18. Kono S, Ikeda M, Tokudome S, Kuratsune M. A case–control study of gastric cancer and diet in northern Kyushu, Japan. *Jpn J Cancer Res* 1988;79:1067–74.
19. Inoue M, Tajima K, Hirose K, Hamajima N, Takezaki T, Kuroishi T, et al. Tea and coffee consumption and the risk of digestive tract cancers: data from a comparative case-referent study in Japan. *Cancer Causes Control* 1998;9:209–16.
20. Koizumi Y, Tsubono Y, Nakaya N, Nishino Y, Shibuya D, Matsuoka H, et al. No association between green tea and the risk of gastric cancer: pooled analysis of two prospective studies in Japan. *Cancer Epidemiol Biomarkers Prev* 2003;12:472–3.
21. Marugame T, Sobue T, Satoh H, Komatsu S, Nishino Y, Nakatsuka H, et al. Lung cancer death rates by smoking status: comparison of the Three-Prefecture Cohort study in Japan to the Cancer Prevention Study II in the USA. *Cancer Sci* 2005;96:120–6.
22. Geleijnse JM, Launer LJ, Hofman A, Pols HA, Witteman JC. Tea flavonoids may protect against atherosclerosis: the Rotterdam Study. *Arch Intern Med* 1999;159:2170–4.
23. Geleijnse JM, Launer LJ, Van der Kuip DA, Hofman A, Witteman JC. Inverse association of tea and flavonoid intakes with incident myocardial infarction: the Rotterdam study. *Am J Clin Nutr* 2002;75:880–6.
24. Miksicek RJ. Estrogenic flavonoids: structural requirements for biological activity. *Proc Soc Exp Biol Med* 1995;208:44–50.
25. Mazur WM, Wähälä K, Rasku S, Salakka A, Hase T, Adlercreutz H. Lignan and isoflavonoid concentrations in tea and coffee. *Br J Nutr* 1998;79:37–45.
26. Cheng TO. Why is green tea more cardioprotective in women than in men? *Int J Cardiol* 2007;122:244.
27. Geleijnse JM, Witteman JC, Launer LJ, Lamberts SW, Pols HA. Tea and coronary heart disease: protection through estrogen-like activity? *Arch Intern Med* 2000;160:3328–9.
28. Hoshiyama Y, Kawaguchi T, Miura Y, Mizoue T, Tokui N, Yatsuya H, et al., Japan Collaborative Cohort Study Group. A nested case–control study of stomach cancer in relation to green tea consumption in Japan. *Br J Cancer* 2004;90:135–8.
29. Sasazuki S, Inoue M, Miura T, Iwasaki M, Tsugane S, Japan Public Health Center-based Prospective Study Group. Plasma tea polyphenols and gastric cancer risk: a case-control study nested in a large population-based prospective study in Japan. *Cancer Epidemiol Biomarkers Prev* 2008;17:343–51.
30. Matsubara S, Shibata H, Ishikawa F, Yokokura T, Takahashi M, Sugimura T, et al. Suppression of *Helicobacter pylori*-induced gastritis by green tea extract in Mongolian gerbils. *Biochem Biophys Res Commun* 2003;310:715–9.
31. Takabayashi F, Harada N, Yamada M, Murohisa B, Oguni I. Inhibitory effect of green tea catechins in combination with sucralfate on *Helicobacter pylori* infection in Mongolian gerbils. *J Gastroenterol* 2004;39:61–3.
32. Myung SK, Bae WK, Oh SM, Kim Y, Ju W, Sung J, et al. Green tea consumption and risk of stomach cancer: a meta-analysis of epidemiologic studies. *Int J Cancer* 2009;124:670–7.
33. Goldbohm RA, Hertog MG, Brants HA, van Poppel G, van den Brandt PA. Consumption of black tea and cancer risk: a prospective cohort study. *J Natl Cancer Inst* 1996;88:93–100.
34. Center for Cancer Control and Information Services [NCC website]. Age-standardized gastric cancer mortality rate, in 2009. http://ganjoho.jp/professional/statistics/statistics.html#04 [cited 3 August 2011].
35. Cheng KK, Day NE. Nutrition and esophageal cancer. *Cancer Causes Control* 1996;7:33–40.
36. Yu GP, Hsieh CC, Wang LY, Yu SZ, Li XL, Jin TH. Green-tea consumption and risk of stomach cancer: a population-based case–control study in Shanghai, China. *Cancer Causes Control* 1995;6:532–8.
37. *The council for Science and Technology, Ministry of Education, Culture, Sports, Science and Technology, Japan: Standard Tables of*

Food Composition in Japan. Fifth revised and enlarged edition. Tokyo: National Printing Bureau 2005.
38. Sun CL, Yuan JM, Lee MJ, Yang CS, Gao YT, Ross RK, et al. Urinary tea polyphenols in relation to gastric and esophageal cancers: a prospective study of men in Shanghai, China. *Carcinogenesis* 2002;23:1497–503.

Appendix

Research group members: Shoichiro Tsugane (principal investigator), Manami Inoue, Shizuka Sasazuki, Motoki Iwasaki, Tetsuya Otani (until 2006), Norie Sawada (since 2007), Taichi Shimazu (since 2007) (National Cancer Center, Tokyo); Ichiro Tsuji (since 2004), Yoshitaka Tsubono (in 2003) (Tohoku University, Sendai); Yoshikazu Nishino (until 2006) (Miyagi Cancer Research Institute, Natori, Miyagi); Akiko Tamakoshi (since 2010) (Aichi medical University, Aichi); Keitaro Matsuo (until 2010), Hidemi Ito (since 2010) (Aichi Cancer Center, Nagoya); Kenji Wakai (Nagoya University, Nagoya); Chisato Nagata (Gifu University, Gifu); Tetsuya Mizoue (National Center for Global Health and Medicine, Tokyo); Keitaro Tanaka (Saga University, Saga).

JJCO Japanese Journal of Clinical Oncology

Public Health Report

Jpn J Clin Oncol 2012;42(1)63–73
doi:10.1093/jjco/hyr170
Advance Access Publication 29 November 2011

Cigarette Smoking and Esophageal Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence Among the Japanese Population

Isao Oze[1], Keitaro Matsuo[1,*], Hidemi Ito[1], Kenji Wakai[2], Chisato Nagata[3], Tetsuya Mizoue[4], Keitaro Tanaka[5], Ichiro Tsuji[6], Akiko Tamakoshi[7], Shizuka Sasazuki[8], Manami Inoue[8] and Shoichiro Tsugane[8] for the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan

[1]Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, [2]Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Nagoya, [3]Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu, [4]Department of Epidemiology and International Health, International Clinical Research Center, National Center for Global Health and Medicine, Tokyo, [5]Department of Preventive Medicine, Saga Medical School, Faculty of Medicine, Saga University, Saga, [6]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, [7]Department of Public Health, Aichi Medical University School of Medicine, Nagakute and [8]Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan

*For reprints and all correspondence: Keitaro Matsuo, 1-1 Kanokoden, Chikusa-ku, Nagoya-city, Aichi 464-8681, Japan. E-mail: kmatsuo@aichi-cc.jp

Received August 8, 2011; accepted October 31, 2011

Objective: Although cigarette smoking is considered as an important risk factor for esophageal cancer, the magnitude of the association might be varied among geographic areas. Therefore, we reviewed epidemiologic studies on the association between cigarette smoking and esophageal cancer among the Japanese population.

Methods: Original articles were obtained from MEDLINE searched using PubMed or from searches of the *Ichushi* database, complemented by manual searches. Evaluation of associations was based on the strength of evidence ('convincing', 'probable', 'possible' or 'insufficient') and the magnitude of association ('strong', 'moderate', 'weak' or 'no association'), together with biological plausibility as previously evaluated by the International Agency for Research on Cancer.

Results: We identified four cohort studies and 11 case–control studies. All cohort studies and eight case–control studies showed strong positive associations between esophageal cancer and cigarette smoking. All cohort studies and five case–control studies showed that cigarette smoking had dose–response relationships with esophageal cancer. Meta-analysis of 12 studies indicated that the summary estimate for ever smokers relative to never smokers was 3.01 (95% confidence interval: 2.30–3.94). Summary relative risk for current and former smokers relative to never smokers was 3.73 (2.16–6.43) and 2.21 (1.60–3.06), respectively.

Conclusions: We conclude that there is convincing evidence that cigarette smoking strongly increases the risk of esophageal cancer in the Japanese population.

Key words: systematic review – epidemiology – cigarette smoking – esophageal cancer – Japanese

BACKGROUND

Consistent positive associations between cigarette smoking and esophageal cancer were reported from all over the world. In previous comprehensive risk evaluation by the Office of Surgeon General, the risk among current smokers was up to seven or eight times higher than the risk for lifetime non-smokers (1). In the most recent evaluation by the International Agency for Research on Cancer (IARC), cigarette smoking was evaluated as Group 1: carcinogenic to humans (2,3). Thus, cigarette smoking is a well-established risk factor for esophageal cancer.

On the other hand, the risk of esophageal cancer might vary among geographic areas. In addition, the distribution of histologic subtypes differs across countries. Squamous cell carcinoma is still prevalent in Japanese population, whereas adenocarcinoma is getting prevalent in Western population (4–7). The variability in cigarette consumption or in composition of ethnicities might be the causes of the difference. Therefore, the magnitude of association between cigarette smoking and esophageal cancer among Japanese population might differ from the other regions.

We reviewed epidemiologic studies on cigarette smoking and esophageal cancer risk among Japanese. This report is one of a series of articles by our research group (8–14), which is investigating the association between lifestyle and the major types of cancer in Japan.

PATIENTS AND METHODS

Searching of Subject Researches

The details of the evaluation method have been described elsewhere (8). In brief, original articles for this review were identified through searches of the MEDLINE (PubMed) and *Ichushi (Japana Centra Revuo Medicina)* databases, complemented by manual searches of references from relevant articles where necessary. All epidemiologic studies on the association between cigarette smoking and esophageal cancer incidence/mortality among the Japanese from 1950 (or 1983 for the *Ichushi* database) to June 2011, including papers in press if available, were identified using the following as keywords: cigarette, smoking, esophagus, esophageal cancer, cohort, follow-up, case-control, Japan and Japanese. Papers written in either English or Japanese were reviewed, and only studies on Japanese populations living in Japan were included. The individual results were summarized in the tables separately as cohort or case–control studies. In the case of multiple publications of analyses of the same or overlapping data sets, only data from the largest or the most recent studies were included.

Evaluation of Strength of Association Between Cigarette Smoking and Esophageal Cancer Risk

The evaluation was made based on the magnitudes of association and the strength of evidence. First, the former was assessed by classifying the relative risk (RR) in each study into the following four categories, while considering statistical significance (SS) or no statistical significance (NS), as strong (symbol ↓↓↓ or ↑↑↑), <0.5 or >2.0 (SS); moderate (symbol ↓↓ or ↑↑), either (i) <0.5 or >2.0 (NS), (ii) >1.5–2 (SS) or (iii) 0.5 to <0.67 (SS); weak (symbol ↓ or ↑), either (i) >1.5–2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association (symbol –), 0.67–1.5 (NS). When the multiple RRs were shown in the single study, we considered the largest RR. Criteria for the magnitude of association are summarized in Table 1. After this process, the strength of evidence was evaluated in a manner similar to that used in the WHO/FAO Expert Consultation Report (15), where evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. In brief, the following criteria were used (8): convincing: evidence based on a substantial number between exposure and disease, with little or no evidence to the contrary, with a biologically plausible association. Probable: evidence based on epidemiologic studies showing fairly consistent associations, but with perceived shortcomings in the available evidence or some evidence to the contrary that precludes a more definite judgment. Possible: evidence based mainly on findings from case–control and cross-sectional studies, requiring more studies to support the tentative associations, which should also be biologically plausible. Insufficient: evidence based on findings of a few studies that are suggestive, but insufficient to establish an association, requiring more well-designed research to support the tentative associations. We assumed that biological plausibility corresponded to the judgment of the recent evaluation from the IARC (2,3). The final judgment is made based on the consensus of research group members.

Quantitative Evaluation of Association by Meta-analysis

In addition, when there was 'convincing' or 'probable' evidence of a positive or inverse association, meta-analysis was

Table 1. Evaluation of the magnitude of association in the present report

Magnitude of association	Definition	Statistical significance	Symbol
Strong	RR < 0.5 or RR > 2.0	SS	↑↑↑ or ↓↓↓
Moderate	RR < 0.5 or RR > 2.0	NS	↑↑ or ↓↓
	1.5 < RR ≤ 2.0	SS	
	0.5 ≤ RR < 0.67	SS	
Weak	1.5 < RR ≤ 2.0	NS	↑ or ↓
	0.5 ≤ RR < 0.67	NS	
	0.67 ≤ RR ≤ 1.5	SS	
No association	0.67 ≤ RR ≤ 1.5	NS	—

RR, relative risk; SS, statistically significant; NS, not statistically significant.

conducted to obtain summary estimates of the association. In general, studies that reported RRs and their confidence intervals (CIs) by comparing ever smokers with never smokers were included in the meta-analysis. In case the subject study reported RRs separately according to multiple smoking status or levels, we estimated summary RR for ever smokers relative to never smokers by meta-analysis within the study and the study-specific summary RR was included in the final meta-analysis. Studies without information on CIs and different reference categories were excluded from meta-analysis. General variance-based methods were used to estimate summary statistics and their 95% CIs. Heterogeneity among studies was examined by testing the Q-statistic (16), with the model used to determine summary RR and its 95% CI, namely a random- or fixed-effect model, selected according to the significance in the Q-statistic. Publication bias was assessed by using the funnel plot and Egger's test (17). Meta-analysis was done using the 'metan' and 'metabias' command of STATA statistical package version 10 (Stata Corp. LP, College Station, TX, USA).

MAIN FEATURES AND COMMENTS

After excluding 2 cohort studies (18,19) and 1 case–control study (20) due to the analysis of the overlapping datasets, we identified 4 cohort studies (21–24) (Table 2) and 11 case–control studies (25–35) (Table 3). Of these cohort studies, one (21) presented the results by sex and three (22–24) presented the results for men only. Among case–control studies, one (26) presented the results by sex, five (25,29,30,34,35) for men and women combined, three (27,28,31) for men only and two (32,33) for women only.

A summary of the magnitude of association for the cohort studies and case–control studies was shown in Tables 4 and 5, respectively. All cohort studies (21–24) and 8 of 11 case–control studies (25,26,28,29,31,33–35) showed strong positive association between cigarette smoking and esophageal cancer. Moreover, the dose–response relationships between cigarette smoking and esophageal cancer risk were shown in all cohort studies (21–24) and five case–control studies (25,28,29,33,35). Only one cohort study (21) and one case–control study (28) showed the reversal of risk after smoking cessation. The RRs for years of quitting smoking were inconsistent between two studies.

We conducted a meta-analysis to clarify the magnitude of cigarette smoking among Japanese (Figs 1 and 2). Two studies were excluded because of the different reference category (31,34). The random-effect model was selected for the meta-analysis because heterogeneity tested for Q-statistics was significant ($Q = 42.59$, $P < 0.001$). Although Egger's test for publication bias was not significant ($P = 0.148$), funnel plot showed asymmetry (Fig. 3). Ever smokers had significantly higher summary RR than never smokers (RR 3.01, 95% CI 2.30–3.94) (Fig. 1). Seven studies (22–24,27–30) showed the RR of current and former smokers compared with never smokers. Summary RR for current and former smokers were 3.73 (95% CI, 2.16–6.43) and 2.21 (1.60–3.06), respectively (Fig. 2). When we limit the analysis to cohort studies, summary RRs for ever smokers and current smokers were 2.97 (95% CI, 2.12–4.16) and 4.20 (2.83–6.23), respectively. Several studies did not adjusted alcohol consumption in their analyses; therefore, we conducted the meta-analysis only among the studies adjusted for alcohol consumption. After excluding seven studies (21,22,25,26,29,30,33) without adjustment for alcohol drinking, summary RR for ever smokers was 2.70 (95% CI, 1.64–4.45), although heterogeneity was significant ($Q = 27.16$, $P < 0.001$).

There were several potential limitations in the Japanese studies reviewed here. One methodological issue was assessment of smoking exposures. Information on cigarette consumption was investigated by questionnaire in all cohort and case–control studies. However, the different categorization of smoking exposure was used in each questionnaire (e.g. smoking status, pack years, number of cigarettes a day). In addition, different definitions of smoking status were used. For example, former smokers with a short duration of smoking cessation were sometimes classified as current smokers. These might attenuate the association between cigarette smoking and esophageal cancer risk. In contrast, recall bias might intensify the association. The magnitude of the effects by these methodological issues may be small to influence the current observation.

Meta-analysis showed that ever smokers had significantly higher risk for esophageal cancer than never smokers. The asymmetrical appearance of the funnel plot and small P value for Egger's test suggested the existence of publication bias. Thus, summary RR of 3.01 might be overestimated. As the quantitative measurement of cigarette consumption was heterogeneous across studies, we could not see the dose–response relationships. The heterogeneity across studies is likely to be due to the different cigarette consumption levels by characteristics of subjects in each study, such as birth cohort, age, sex and base population. Moreover, only a little evidence was available about smoking cessation for esophageal cancer in Japanese population. Therefore, a pooled analysis using common cigarette consumption categories is warranted.

EVALUATION OF EVIDENCE ON CIGARETTE SMOKING AND ESOPHAGEAL CANCER RISK IN JAPANESE

From these results, and on the bases of assumed biological plausibility, we conclude that there is convincing evidence that cigarette smoking strongly increases the risk of esophageal cancer in the Japanese population.

Table 2. Cigarette smoking and esophageal cancer risk, cohort studies among Japanese population

Author	Reference	Study period	Study population									
			Number of subjects for analysis, sex, age	Source of subjects	Event followed	Number of incident cases or deaths	Category	Number among cases	Relative risk (95% CI)	*P* value for trend	Confounding variables considered	Comments
Hirayama	21	1965–81	122 261 men	Population-based	Death	438 men	Smoking status			Not described	Age	Follow-up by death certificates, residential registry, 90% confidence intervals
			142 857 women				Non-smoker		1.0			
			≥40 years old				Daily smoker		2.24 (1.72–2.91)			
							Number of cigarettes/day					
							Non-smoker		1.0			
							1–9		1.62 (1.09–2.41)			
							10–19		2.04 (1.54–2.71)			
							≥20[a]		2.69 (2.05–3.53)			
							Age at start of smoking					
							Non-smoker		1.0			
							19 or below		1.61 (1.08–2.40)			
							20 or above		2.30 (1.76–3.00)			
							Years after smoking cessation					
							Non-smoker		1.0			
							1–4		1.53 (0.70–3.38)			
							5–9		1.13 (0.35–3.64)			
							≥10		1.96 (0.88–4.38)			
						147 women	Smoking status					
							Non-smoker		1			
							Daily smoker		1.75 (1.21–2.51)			
							Number of cigarettes/day					
							Non-smoker		1			
							1–9		1.74 (1.04–2.91)			
							10–19[a]		2.45 (1.53–3.93)			
							≥20		NA			
							Age at start of smoking					
							Non-smoker		1			
							19 or below		0			
							20 or above		1.83 (1.22–2.73)			
							Years after smoking cessation					
							Non-smoker		1			
							1–4		NA			
							5–9		NA			
							≥10		NA			

Sakata et al.	22	1988–99	46 465 men 40–79 years	Population-based 45 areas in Japan JACC study	Death	100 men	Smoking status			Not described	Adjusted for age and centers
							Non-smokers	7	1.0		
							Ex-smokers	25	2.71 (1.16–6.36)		
							Smokers	68	4.36 (2.00–9.52)		
							Age at start of smoking			0.391	
							Non-smokers	7	1.0		
							25+	13	3.85 (1.54–9.64)		
							20–24	38	4.89 (1.98–12.07)		
							10–19	13	3.24 (1.06–9.89)		
							Cigarettes smoked per day			0.431	
							Non-smokers	7	1.0		
							1–10 cigarettes/day	15	5.11 (2.07–12.65)		
							11–20 cigarettes/day	39	4.42 (1.97–9.92)		
							21–30 cigarettes/day	8	3.19 (1.11–9.19)		
							≥30 cigarettes/day	5	4.33 (1.25–14.99)		
							Years of smoking			0.014	
							Non-smokers	7	1.0		
							≤25.0	4	2.05 (0.42–9.98)		
							25.1–35.0	13	3.54 (1.27–9.89)		
							35.1–45.0[a]	32	5.34 (2.32–12.30)		
							≥45.1	15	4.85 (1.62–14.53)		
							Cumulative amount of smoking			0.086	
							Non-smokers	7	1.0		
							1–19.9 PYs	6	3.24 (1.06–9.89)		
							20.0–29.9 PYs	16	4.89 (1.98–12.07)		
							30.0–39.9 PYs	14	3.85 (1.54–9.64)		
							≥40.0 PYs	28	4.86 (2.11–11.21)		
Ishikawa et al.	23	Cohort 1 1984–92 Cohort 2 1990–97	Cohort 1 9008 men ≥40 years old Cohort 2 17 715 men 40–64 years	Population-based Miyagi pref.	Incidence	Cohort 1 38 cases Cohort 2 40 cases	Cohort 1 Category of smoking			0.008	Adjusted for age, alcohol drinking, green tea, coffee and black tea
							Never	2	1.0		
							Former	6	2.49 (0.50–12.44)		
							1–19 cigarettes/day	11	5.39 (1.18–24.61)		
							≥20 cigarettes/day	19	5.48 (1.24–24.18)		
							Cohort 2				
							Category of smoking			0.006	
							Never	2	1.0		
							Former	5	1.72 (0.33–8.92)		
							1–19 cigarettes/day	10	4.63 (1.01–21.30)		
							≥20 cigarettes/day	23	4.73 (1.10–20.34)		

Continued

Table 2. *Continued*

Author	Reference	Study period	Study population									
			Number of subjects for analysis, sex, age	Source of subjects	Event followed	Number of incident cases or deaths	Category	Number among cases	Relative risk (95% CI)	*P* value for trend	Confounding variables considered	Comments
							Pooled 1 and 2					
							Category of smoking			0.0001		
							Never	4	1.0			
							Former	11	2.07 (0.66–6.57)			
							1–19 cigarettes/day	21	5.00 (1.70–14.66)			
							≥20 cigarettes/day[a]	42	5.09 (1.80–14.40)			
Ishiguro et al.	24	Cohort 1 1990–2004 Cohort 2 1993–2004	Cohort 1 + 2 60 876 men ≥40 years old	Population-based JPHC	Incidence	Cohort 1 + 2 215 cases	Cohort 1 + 2 Smoking status				Adjusted for age, area, BMI, preference of hot foods and drinks, ethanol consumption and flushing response	
							Never	14	1			
							Past	61	3.27 (1.78–5.99)			
							Current	140	3.69 (2.07–6.58)			
							Pack-years			0.001		
							<20	26	2.07 (1.07–4.00)			
							20–29	34	2.71 (1.44–5.11)			
							30–39	45	2.97 (1.61–5.48)			
							≥40[a]	95	4.81 (2.72–8.53)			
							Cigarettes/day among current smoker			0.001		
							<20	35	2.77 (1.43–5.34)			
							20–39	87	4.00 (2.21–7.22)			
							≥40	18	4.76 (2.31–9.81)			

NA, not available.
[a]Categories from which the magnitude of association was judged.