JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2014;44(3)282–295
doi:10.1093/jjco/hyt203
Advance Access Publication 22 January 2014

Public Health Report

Soy Intake and Breast Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence Among the Japanese Population

Chisato Nagata[1,*], Tetsuya Mizoue[2], Keitaro Tanaka[3], Ichiro Tsuji[4], Akiko Tamakoshi[5], Keitaro Matsuo[6], Kenji Wakai[7], Manami Inoue[8,9], Shoichiro Tsugane[8] and Shizuka Sasazuki[8], for the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan

[1]Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu, [2]Department of Epidemiology and International Health, Research Institute, International Medical Center of Japan, Tokyo, [3]Department of Preventive Medicine, Saga Medical School, Faculty of Medicine, Saga University, Saga, [4]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, [5]Department of Public Health, Hokkaido University Graduate School of Medicine, Sapporo, [6]Department of Preventive Medicine, Kyushu University Faculty of Medical Sciences, Fukuoka, [7]Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Nagoya, [8]Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo and [9]AXA Department of Health and Human Security, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

*For reprints and all correspondence: Chisato Nagata, Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan. E-mail: chisato@gifu-u.ac.jp

Received August 5, 2013; accepted December 2, 2013

Objective: We reviewed epidemiological studies of soy intake and breast cancer among Japanese women. This report is one among a series of articles by our research group, which is evaluating the existing evidence concerning the association between health-related lifestyles and cancer.

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 biological plausibility.

Results: Five cohort studies and six case–control studies were identified. Among the cohort studies, two studies observed that total soy intake (in terms of total amounts of soy foods or soy isoflavones) was associated with a moderate ($0.5 \leq$ relative risk ≤ 0.67 with statistical significance) or strong (relative risk ≤ 0.5 with statistical significance) risk reduction of breast cancer in postmenopausal women. Among the case–control studies, two studies reported a weak ($0.67 \leq$ odds ratio ≤ 1.5 with statistical significance or $0.5 \leq$ odds ratio ≤ 0.67 without statistical significance) inverse association between total soy intake and the risk of breast cancer. In the former, this association was observed in all women combined—premenopausal and postmenopausal women—but in the latter, the association was confined to postmenopausal women. The associations of intakes of individual soy foods with the risk of breast cancer were generally null. There is some evidence that supports the biological plausibility of a protective effect of isoflavones on breast cancer risk.

Conclusions: We conclude that soy intake possibly decreases the risk of breast cancer among Japanese women.

Key words: systematic review – epidemiology – dietary soy – breast cancer – Japanese

BACKGROUND

The role of diet in the risk of breast cancer is of importance as a potentially modifiable risk factor. There has been much interest in the potential of soy foods to reduce the risk of breast cancer. Soybeans are the predominant source of isoflavones, the main class of phytoestrogen. Estrogen is an important determinant of breast cancer risk (1). The estrogenic activity of isoflavones has been expected to exert antiestrogenic effects (2). Several laboratory studies have indicated that soy isoflavones have anticarcinogenic effects (3). Epidemiological studies have examined the association between soy intake and the risk of breast cancer, but there has been no consensus regarding the preventive aspects of soy. Previous meta-analyses of observational studies suggest that the inverse association between soy intake and the risk of breast cancer is confined to Asian populations (4,5). Soy intake varies by ethnicity; data suggest that the average consumption of soy in terms of isoflavones in the USA and Europe is 1–2 mg/day, whereas in Asian countries, the average intake is over 10 mg/day (6). The type of soy that Asians and Americans or Europeans eat is quite different. In Asian countries, soy foods are generally minimally processed and often fermented. However, in western countries, the consumption of traditional soyfoods is substantially lower and a portion of total isoflavone consumption is derived from soy protein and soy flour added to a variety of foods (7). These factors are thought to contribute to the heterogeneity in results of soy intake and breast cancer risk across studies. Even in Asian countries, soy intake and sources vary among regions (6,8,9). Therefore, to develop public health nutrition policies in Japan, it is of essential value to summarize the current evidence from epidemiological studies in the Japanese population.

We reviewed epidemiological studies of soy intake and breast cancer among the Japanese population. This report is one among a series of articles by our research group, which is investigating the associations between lifestyles and major types of cancer in Japan (10).

PATIENTS AND METHODS

Epidemiological studies of the association between soy intake and breast cancer incidence or mortality among Japanese were identified through a MEDLINE search from 1980 to July 2013 using the terms ‘breast cancer’, ‘Japan’ and ‘soy’ or ‘diet’. A search of the Ichushi (Japana Centra Revuo Medicina) database was also done to identify the studies written in Japanese from 1983 to July 2013. For inclusion into the review, studies had to be analytic epidemiological studies written either in English or in Japanese and include Japanese populations living in Japan. In the case of multiple publications of analyses of the same or overlapping datasets, only data from the largest or most updated results had to be included. Incidence is given priority over mortality as an outcome measure. Details of the evaluation methods are presented elsewhere (10).

Results from each study were summarized in the tables separately by study design as cohort or case–control studies. Relative risks (RRs) or odds ratios (ORs) in each epidemiologic study were grouped by magnitude of association, with consideration to statistical significance (SS) or no statistical significance (NS), as strong, <0.5 or >2.0 (SS); moderate, (1) <0.5 or >2.0 (NS), (2) >1.5 to 2 (SS) or (3) 0.5 to <0.67 (SS); weak, (1) >1.5 to 2 (NS), (2) 0.5 to <0.67 (NS) or (3) 0.67 to 1.5 (SS) or no association, 0.67–1.5 (NS). For this categorization, we referred to the criteria described in the expert panel report published in 1997 (11). Although the expert report used 1.5 or 0.75 as the cut-off value between ‘moderate’ and ‘weak’, we adopted the reciprocal of 1.5 ($=0.67$) instead of 0.75. We mainly used the RR or OR for the highest intake category. After this process, the strength of evidence was evaluated in a similar manner to that used in the WHO/FAO Expert Consultation Report (12), in which evidence was classified as ‘convincing’, ‘probable’, ‘possible’ and ‘insufficient’. We assumed that biological plausibility based on evidence in experimental models, human studies and other relevant data.

MAIN FEATURES AND COMMENTS

We identified five cohort studies (13–17) and six case–control studies (18–23) (Tables 1 and 2). Details of the component studies including age range, study period, numbers of women enrolled, RR or OR of breast cancer for total soy intake (in terms of total amounts of soy foods or isoflavones) or intake of individual soy food and covariates used in adjustments are given. When analyses stratified according to menopausal status were available, the results were shown separately for premenopausal and postmenopausal women. As only two studies took account of receptor status, results according to receptor status were not shown. Summaries of the magnitudes of association for each study are shown in Tables 3 and 4.

Two (15,17) of the five cohort studies estimated total soy intake, and the estimates were based on the use of a validated food frequency questionnaire (FFQ). Both studies observed a significant inverse association between soy isoflavone intake and the risk of breast cancer. The remaining cohort studies did not observe a significant inverse association between any specific soy food items and the risk of breast cancer. Separate analyses according to menopausal status at the baseline were conducted in the study by Yamamoto et al. (15). In their study, the inverse association between soy isoflavone intake and the risk of breast cancer was stronger in postmenopausal women (15). Another study reported by Wada et al. (17) taking into account menopausal status during the follow-up period observed a significant risk reduction associated with soy isoflavone intake in postmenopausal but not premenopausal women.

Only one study (22) out of the six case–control studies observed a significant inverse association between soy intake and the risk of breast cancer. This study estimated to total soy

Table 1. Breast cancer risk and soy intake in cohort studies of Japanese women

References		Study period	Study population				Category	Number among cases	Relative risk (95%CI or *P* value)	*P* value for trend	Confounding variables considered	Comments
Author	Year		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
Hirayama (13)[a]	1990	1966–82	1 42 857	General population (six-prefecture cohort)	Mortality	241	Miso soup				Adjusted for: age	
							Non-daily		1.00			
							Daily		0.85 (0.68–1.06)			
Key et al. (14)	1999	1969–93	34 759	Atomic-bomb survivors	Incidence	427	Tofu				Adjusted for: age, calendar period, city and age at time of bombing and radiation dose	
							≤1/week	139	1.00			
							2–4/weeks	199	0.99 (0.80–1.24)			
							≥5 weeks	52	1.07 (0.78–1.47)	0.71		
							Miso soup					
							≤1/week	134	1.00			
							2–4/weeks	130	1.03 (0.81–1.31)			
							≥5 weeks	123	0.87 (0.68–1.12)	0.31		
Yamamoto et al. (15)	2003	1990–99	21 852	General population (JPHC study)	Incidence	179	Miso soup				Adjusted for: age, area, age at menarche, no. of pregnancies, age at first pregnancy, active and passive smoking, alcohol consumption, physical activity, education level, total energy and meat, fish, vegetable and fruit consumption	
							<1 cup/day	51	1.00			
							1 cup/day	39	1.1 (0.67–1.7)			
							2 cups/day	58	0.74 (0.46–1.2)			
							≥3 cups/day	31	0.60 (0.34–1.1)	0.042		
							Soy foods					
							<2 times/week	38	1.00			
							3–4 times/week	60	0.83 (0.52–1.3)			
							Almost daily	81	0.81 (0.49–1.3)	0.44		
							Isoflavones					
							Q1	44	1.00			
							Q2	50	0.76 (0.47–1.2)			

							Q3	52	0.90 (0.56–1.5)		
							Q4	33	0.46 (0.25–0.84)	0.043	
						Premenopausal	Isoflavones				
							Q1	21	1.00		
							Q2	29	1.0 (0.50–2.0)		
							Q3	29	1.6 (0.79–3.1)		
							Q4	10	0.66 (0.25–1.7)	0.97	
						Postmenopausal	Isoflavones				
							Q1	22	1.00		
							Q2	21	0.58 (0.29–1.1)		
							Q3	23	0.50 (0.25–1.0)		
							Q4	21	0.32 (0.14–0.71)	0.006	
Nisho et al. (16)	2007	1988–90	30 454	General population (JACC study)	Incidence	145	Tofu				Adjusted for: age, study area, family history of breast cancer, age at menopause, age at first birth, parity, use of exogenous female hormone, smoking, consumption of green leafy vegetables, walking time, body mass index and total energy intake
							<3 times/week	44	1.00	0.55	
							3–4 times/week	52	1.17 (0.77–1.78)		
							Almost daily	49	1.14 (0.74–1.77)		
							Boiled beans				
							<1 time/week	87	1.00	0.31	
							1–2 times/week	36	0.91 (0.61–1.37)		
							≥3 times/week	22	0.77 (0.47–1.27)		
							Miso soup				
							<1 time/day	46	1.00	0.94	
							1 cup/day	38	0.92 (0.59–1.43)		
							≥2 cups/day	61	1.01 (0.65–1.56)		
						Postmenopausal	Tofu				
							≤2 times/week	24	1.00	0.23	
							3–4 times/week	36	1.64 (0.96–2.81)		
							Almost daily	32	1.43 (0.81–2.52)		
							Boiled beans				
							<1 time/week	49	1.00	0.75	
							1–2 times/week	26	1.03 (0.63–1.70)		
							≥3 times/week	17	0.89 (0.50–1.59)		

Continued

Table 1. *Continued*

References		Study period	Study population				Category	Number among cases	Relative risk (95%CI or *P* value)	*P* value for trend	Confounding variables considered	Comments
Author	Year		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
							Miso soup					
							<1 cup/day	31	1.00	0.76		
							1 cup/day	26	0.99 (0.57–1.71)			
							≥2 cups/day	35	0.92 (0.52–1.62)			
Wada et al. (17)	2013	1992–2008	15 607	General population (Takayama study)	Incidence	172	Soy intake				Adjusted for: age, body mass index, physical activity score, smoking status, alcohol consumption, education years, age at menarche, age at first delivery, menopausal status, parity, history of hormone-replacement therapy and total energy intake	
							Q1	56	1.00			
							Q2	39	0.72 (0.48–1.08)			
							Q3	39	0.71 (0.47–1.08)			
							Q4	38	0.72 (0.47–1.10)	0.14		
							Isoflavone intake					
							Q1	58	1.00			
							Q2	34	0.61 (0.40–0.94)			
							Q3	44	0.80 (0.53–1.18)			
							Q4	36	0.67 (0.44–1.03)	0.25		
						Premenopausal	Soy intake					
							Q1	13	1.00			
							Q2	10	0.92 (0.40–2.12)			
							Q3	7	0.79 (0.31–2.01)			
							Q4	8	1.10 (0.45–2.68)	0.18		
							Isoflavone intake					
							Q1	12	1.00			
							Q2	7	0.71 (0.31–2.01)			
							Q3	10	1.26 (0.54–2.95)			
							Q4	9	1.52 (0.63–3.65)	0.14		

Postmenopausal	Soy intake				
	Q1	43	1.00		
	Q2	29	0.65 (0.41–1.05)		
	Q3	32	0.67 (0.42–1.07)		
	Q4	30	0.63 (0.39–1.01)	0.023	
	Isoflavone intake				
	Q1	46	1.00		
	Q2	27	0.57 (0.35–0.92)		
	Q3	34	0.68 (0.44–1.07)		
	Q4	27	0.52(0.32–0.85)	0.046	

CI, confidence interval; Q, quartile.
[a]No. of cases for each intake category is not available.

intake in terms of total amount of soy foods. Additional two studies (18,23) estimated total soy intake (in terms of soy fat in one study). One of them observed a weak inverse association in postmenopausal women (23) and the other observed nearly null association (18).

Since the principal forms of isoflavone differ between fermented and unfermented soy foods, there is a hypothesis that the form or source of isoflavone might affect the association between soy intake and breast cancer risk (24). However, the associations of most of individual soy food intake with the risk of breast cancer were null in the component studies. For miso, a fermented soy food, one cohort study observed a significant inverse association (15), but one case–control study observed a significant positive association (20). The latter study reported that there was no significant association when premenopausal and postmenopausal women were separately analyzed (20).

In the present review, a protective effect of soy intake on breast cancer was suggested in some but not all studies. Although a positive association was observed in some studies, the association was weak and limited to certain food items or subgroups. In western countries, there has been concern about possible promotive effects of soy on breast cancer. This concern is primarily based on *in vitro* and rodent data which suggest that genistein can stimulate tumor cell proliferation (25,26). The present data indicate that the amount consumed by Japanese is not detrimental to breast health. Although the present review focused on studies regarding soy intake and the risk of breast cancer, another study (a nested case–control study in a JPHC cohort) (27) utilized biomarkers of total soy intake, i.e. plasma isoflavone. This study demonstrated a significant inverse association between serum isoflavone level and the risk of breast cancer, which also supports a potential protective effect of soy intake. In a subsample from this cohort, Spearman correlation coefficient between plasma isoflavone level and isoflavone intake estimated from FFQ was 0.31 (28). Similar values for the correlations between blood or urinary isoflavone level and dietary intake estimated from FFQ or diet records have been reported from other studies (29–31).

Since three studies (15,17,23) revealed that the inverse association of soy intake with the risk of breast cancer was observed only in postmenopausal women or was stronger in postmenopausal women than in premenopausal women, menopause status appears to modify the association between soy intake and the risk of breast cancer. Hormone profile, such as low endogenous estrogen levels in postmenopausal women, may be relevant. However, in a recent meta-analysis of intervention studies, soy or isoflavone consumption was associated with a small but non-significant increase in total estradiol (32).

In 2008, the meta-analysis of eight studies (one cohort and seven case–control studies) conducted in Asia showed an inverse association of soy intake and the risk of breast cancer; the combined RR for highest ($\geq$20 mg of isoflavone per day) vs. lowest ($\leq$5 mg of isoflavone per day) was 0.71

Table 2. Breast cancer risk and soy intake in case–control studies of Japanese women

References		Study time	Study subjects				Category	Relative risk (95%CI or p)	*P* for trend	Confounding variables considered
Author	Year		Type and source	Definition	Number of cases	Number of controls				
Hirohata et al. (18)	1985	Not given	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	Fat from soy	Mean		Matched (1:2) for : Age (± 5 years); Adjusted for: age,weight, menopause, and parity.
							Cases	26 g/week		
							Controls			
							Hospital	22 g/week		
							Neighborhood	26 g/week		
Kikuchi et al. (19)	1990	1988–1989	Hospital-based (2 hospitals)	Cases: histologically confirmed cases Controls: hospital controls and participans in breast cancer screening	49	49	Tofu and soybeans			Matched (1:1) for age(± 3 years)
							Low	1.00		
							High	0.90*		
Masuoka et al. (20)	1991	1986–1989	Hospital-based	Cases: primary breast cancer patients Controls: neighborhood controls selected from telephone directories	152	304	Miso soup			
							times/day	1.41*	<0.05	Matched (1:2) for age (± 2) and menopausal status; Adjusted for: consumption of ramen noodles, meat, beef,chiken, fish, black tea, shochu, and wine.
					67 postmenopausal	134 postmenopausal	times/day	1.27 (0.82–1.96)		Matched (1:2) for age (± 2) and menopausal status; Adjusted for: consumption of potatoes, and meat.
Hirose et al. (21)	1995	1988–1992	Hospital-based (Aichi Cancer Center)	Cases: primary breast cancer detected by histological exsamination Controls: cancer-free			Miso soup			Adjusted for: age and first-visit year
					607 premenopausal	14883 premenopausal	Occasional/none	1.00		
							Daily	1.16 (0.98–1.37)		
					443 postmenopausal	6192 postmenopausal	Occasional/none	1.00		
							Daily	0.96 (0.78–1.17)		

Suzuki et al. (22)	2008	2001–2005	Hospital-based (Aichi Cancer Center)	Cases: underwent surgical excision and histologically confirmed Controls: cancer-free	678	3390	Soybean products			Matched (1:5) for age (± 0) and menopausal status; Adjusted for: drinking habit, BMI, regular exercise, family history of breast cancer, total nonalcohol energy intake, multivitamin use, age at menarche, parity, hormone-replacement therapy, referral pattern to the hospital.
							Tertile 1	1.00		
							Tertile 2	0.95 (0.77–1.16)		
							Tertile 3	0.80 (0.64–0.99)	0.03	
							Miso soup			
							≤2 times/month	1.00		
							3–6 times/week	0.97 (0.79–1.20)		
							≥1 time/week	0.99 (0.79–1.24)	0.93	
							Tofu			
							≤3 times/month	1.00		
							1–2 times/week	0.98 (0.80–1.21)		
							≥3 times/week	0.89 (0.72–1.12)	0.3	
							Natto			
							≤3 times/month	1.00		
							1–2 times/week	0.96 (0.78–1.19)		
							≥3 times/week	0.87 (0.70–1.08)	0.2	
							Aburage			
							Seldom	1.00		
							1–3 times/month	1.21 (0.88–1.66)		
							>1 time/week	1.11 (0.80–1.54)	0.99	
					329 premenopausal	1645 premenopausal	Soybean products			
							Tertile 1	1.00		
							Tertile 2	0.85 (0.64–1.13)		
							Tertile 3	0.74 (0.54–1.02)	0.06	
							Miso soup			
							≤2 times/month	1.00		
							3–6 times/week	0.89 (0.67–1.18)		
							≥1 time/week	0.91 (0.66–1.27)	0.58	
							Tofu			
							≤3 times/month	1.00		
							1–2 times/week	0.95 (0.71–1.27)		
							≥3 times/week	0.84 (0.61–1.17)	0.32	

Continued

Table 2. *Continued*

References		Study time	Study subjects				Category	Relative risk (95%CI or p)	*P* for trend	Confounding variables considered
Author	Year		Type and source	Definition	Number of cases	Number of controls				
							Natto			
							≤3 times/month	1.00		
							1–2 times/week	1.04 (0.78–1.39)		
							≥3 times/week	0.72 (0.52–0.99)	0.06	
							Aburage			
							Seldom	1.00		
							1–3 times/month	1.10 (0.73–1.65)		
							>1 time/week	1.06 (0.70–1.61)	0.93	
					349 postmenopausal	1745 postmenopausal	Soybean products			Additionally adjusted for age at menopause
							Tertile 1	1.00		
							Tertile 2	1.01 (0.75–1.39)		
							Tertile 3	0.84 (0.61–1.15)	0.17	
							Miso soup			
							≤2 times/month	1.00		
							3–6 times/week	1.07 (0.78–1.47)		
							≥1 time/day	1.08 (0.79–1.48)	0.65	
							Tofu			
							≤3 times/month	1.00		
							1–2 times/week	1.00 (0.73–1.37)		
							≥3 times/week	0.93 (0.68–1.28)	0.56	
							Natto			
							≤3 times/month	1.00		
							1–2 times/week	0.91 (0.66–1.27)		
							≥3 times/week	0.99 (0.72–1.36)	0.95	
							Aburage			
							Seldom	1.00		
							1–3 times/month	1.59 (0.90–2.81)		
							>1 time/week	1.37 (0.78–2.41)	0.97	

Iwasaki et al. (23)	2009	2001–2006	Hospital-based (Nagano)	Cases: histologically confirmed cases; Controls: cancer-free medical check examinees	390	390	Isoflavone		Matched (1:1) for: age (± 3 years) and residential area Adjusted for: menopausal status, number of birth, family history of breast cancer, smoking status, moderate pysical activity in the past 5 years, total energy, and vitamin supplement use.
							Low	1.00	
							Middle	0.86 (0.59–1.27)	
							High	0.83 (0.54–1.28)	
					178 premenopausal	137 premenopausal	Low	1.00	Adjusted for: age and area, number of births, family history of breast cancer, smoking status, moderate physical activity in the past 5 years, total energy, and vitamin supplement use.
							Middle	0.99 (0.58–1.71)	
							High	1.35 (0.72–2.54)	
					212 postmenopausal	253 postmenopausal	Low	1.00	Adjusted for: age and area, number of births family history of breast cancer, smoking status, moderate physical activity in the past 5 years, total energy, and vitamin supplement use.
							Middle	0.79 (0.48–1.29)	
							High	0.62 (0.38–1.01)	

BMI, body mass index.
[a]95% CI is not available.

Table 3. Summary of associations between breast cancer risk and soy intake in cohort studies of Japanese women

References			Study population				Strength of association	
Author	Year	Study period	Number of subjects	Ranged age	Event	Number of incident cases or deaths		
Hirayama (13)	1990	1966–82	1 42 857	40 years or over	Mortality	241	—	Miso soup
Key et al. (14)	1999	1969–93	34 759	NA	Incidence	427	—	Miso soup, tofu
Yamamoto et al. (15)	2003	1990–99	21 852	40–59 years	Incidence	179	↓↓↓	Isoflavones
							↓↓	Miso soup
							—	Other soy foods
						89 premenopausal	↓	Isoflavones
						87 postmenopausal	↓↓↓	Isoflavones
Nisho et al. (16)	2007	1988–90	30 454	40–79 years	Incidence	145	—	Tofu, miso soup, beans
						92 postmenopausal	—	Tofu, miso soup, beans
Wada et al. (17)	2013	1992–2008	15 607	35 years or over	Incidence	172	↓	Isoflavones
							—	All soy foods
						38 premenopausal	↑	Isoflavones
							—	All soy foods
						134 postmenopausal	↓↓	Isoflavones, all soy foods

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

Table 4. Summary of associations between breast cancer risk and soy intake in case–control studies of Japanese women

References			Study subjects			Strength of association	
Author	Year	Study period	Ranged age	Number of cases	Number of controls		
Hirohata et al. (18)	1985	Not given	NA	212	424	—	Soy fat
Kikuchi et al. (19)	1990	1988–1989	30 years or over	49	49	—	Tofu and soybeans
Masuoka and Mori (20)	1991	1986–89	26–72 years (cases)	152	304	↑	Miso soup
				67 postmenopausal	134 postmenopausal	—	Miso soup
Hirose et al. (21)	1995	1988–92	20 years or older	607 premenopausal	14 883 premenopausal	—	Miso soup
				443 postmenopausal	6192 postmenopausal	—	Miso soup
Suzuki et al. (22)	2008	2001–05	18–79 years	678	3390	↓	All soy foods
						—	Miso soup, tofu, natto, aburage
				329 premenopausal	1645 premenopausal	—	All soy foods, miso soup, tofu, aburage
						↓	Natto
				349 postmenopausal	1745 postmenopausal	—	All soy foods, miso soup, tofu, natto, aburage
Iwasaki et al. (23)	2009	2001–06	20–74 years	390	390	—	Isoflavones
				178 premenopausal	137 premenopausal	—	Isoflavones
				212 postmenopausal	253 postmenopausal	↓	Isoflavones

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

(95% CI = 0.60–0.85) (5). The meta-analysis included one cohort (15) study and one case–control (33) study conducted in Japan. Although there was no apparent discrepancy between the results from cohort studies and case–control studies in this review, cohort studies are less affected by selection bias or recall bias than are case–control studies. Since 2008, to our knowledge, two cohort studies of total soy intake and the risk of breast cancer were reported from Asian countries other than Japan (34,35). The RR for higher (above median) vs. lower (below median) isoflavone intake was 0.82 (95% CI = 0.70–0.97) in a study conducted in Singapore (34). The RR for the highest vs. lowest quintile of isoflavone intake was 0.81 (95% CI = 0.61–1.07) in a study conducted in Shanghai (35). Both studies suggested a modest protective effect of soy against breast cancer. However, the association was stronger in postmenopausal women (RR = 0.74, 95% CI = 0.61–0.90) than in premenopausal women (RR = 1.04, 95% CI = 0.77–1.40) in the former (34), but in the latter (35), the association was stronger in premenopausal women (RR = 0.44, 95% CI = 0.26–0.73) than in postmenopausal women (RR = 1.09, 95% CI = 0.78–1.52).

Some laboratory data showed that dietary genistein stimulates growth in the breast cancer cells (25,26). However, data from clinical trials on purified genistein have not shown clear deleterious effects (36). A favored mechanism by which soy isoflavones may influence breast cancer development is via their affinity and competition with endogenous estrogens. In addition, isoflavones have been shown to be anti-proliferative (37), proapoptic (38), antiangiogenic (39), anti-oxidative (40) and anti-inflammatory (41). It is biologically plausible that soy intake is inversely associated with the risk of breast cancer.

Extensive research based on more, methodologically sound, prospective studies with accurate measurement of soy intake is required to conduct a pooled analysis or meta-analysis, which could quantitatively estimate intake level and address the dose–response relationship as well as possible modification by the food source of isoflavones and menopausal status.

EVALUATION OF EVIDENCE ON SOY INTAKE AND BREAST CANCER RISK IN JAPANESE

From these results and on the basis of assumed biological plausibility, we conclude that soy intake possibly decreases the risk of breast cancer among Japanese populations.

Acknowledgements

The authors gratefully acknowledge the assistance of Ms Izumi Suenaga.

Funding

This study was supported by the National Cancer Center Research and Development Fund.

Conflict of interest statement

None declared.

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APPENDIX

Research group members: Shizuka Sasazuki (principal investigator), Shoichiro Tsugane, Manami Inoue, Motoki Iwasaki, Tetsuya Otani (until 2006), Norie Sawada (since 2007), Taichi Shimazu (since 2007), Taiki Yamaji (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) (Hokkaido University, Sapporo); Keitaro Matsuo (until 2010, since 2012), Hidemi Ito (since 2010 until 2011) (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).