

A Meta-Analysis of Soyfoods and Risk of Stomach Cancer: The Problem of Potential Confounders¹

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Abstract

It has been suggested that consumption of soyfoods may be associated with a reduction in risk of various cancers, including nonhormonally dependent cancers. The purpose of this meta-analysis was to examine the relationship between fermented and nonfermented soyfoods and risk of stomach cancer. We searched the reference lists of English language publications of diet and stomach cancer studies that were conducted in Asia or among Asians living in the United States or elsewhere between 1966 and 1999. All of the analytic epidemiological studies that obtained individual data on intake of soyfoods and presented risk estimates of the association between intake of soyfoods and risk of stomach cancer were identified and included in this review. Our pooled analysis of 14 studies with data on fermented soyfoods yielded an odds ratio/relative risk of 1.26 (95% confidence interval, 1.11–1.43) in association with high intake of such foods. In contrast, our pooled analysis of 10 studies with data on nonfermented soyfoods found an odds ratio/relative risk of 0.72 (95% confidence interval, 0.63–0.82) in association with high intake of these foods. However, further analyses suggest that fermented and nonfermented soyfoods may be associated with salt and fruit/vegetable intake, respectively; salt and fruit/vegetable intake are directly associated with stomach cancer risk. In almost all of the studies we reviewed, the possible confounding role of salt, fruit/vegetable, and other dietary factors had not been considered in the soyfood analyses. In conclusion, the role of soyfoods in the etiology of stomach cancer cannot be determined with confidence until the roles of potential confounders, including salt, fruit/vegetables, and other dietary factors, are more adequately adjusted for.

Introduction

Stomach cancer remains a major cancer in terms of both incidence and mortality; worldwide it is the second leading site of

cancer occurrence (1). Countries with a particularly high incidence of this disease include Japan, China, and Korea. Dietary factors have been recognized as playing an important role in the etiology of stomach cancer. Most epidemiological studies (particularly case-control studies) show that high intake of nitrates and related compounds and salted foods increase the risk whereas high intake of fruits and vegetables lowers the risk of this cancer (2).

In recent years, the role of soybeans in the etiology of stomach cancer has also been of considerable interest (3). Soybeans are an abundant source of isoflavones (4). Although many investigators have focused on the antiestrogenic properties of isoflavones in possibly preventing hormonally mediated cancers (5), isoflavones are antioxidants (6) and possess other antitumor activities, including inhibition of angiogenesis (7), topoisomerase (8), and tyrosine kinase (9). In *in vitro* studies inhibition of the cell growth of stomach cancer cell lines by genistein has also been reported (10). Thus, high intake of soyfoods may reduce the risk of nonhormonally dependent cancers as well as hormonally dependent cancers.

There are two main categories of traditional soyfoods: nonfermented and fermented soyfoods. The main nonfermented soyfoods include soymilk, tofu (bean curd), soybeans, and soynuts; they are consumed mainly for nourishment. The main fermented soyfoods include soy paste (miso in Japan) and fermented soybeans (natto in Japan); fermented soy pastes are generally used as condiments in cooking or making soups, whereas fermented soybeans are also consumed as part of the meal (11). Fermented soy paste is generally high in salt content (11). In a review of soy and cancer, Messina *et al.* (3) suggested that there was an inconsistent relationship between intake of soyfood and stomach cancer; the risk seemed to increase with intake of fermented soyfoods (mainly miso) and decrease with intake of nonfermented soyfoods (mainly tofu).

We have conducted a quantitative review of published studies of the association of fermented and nonfermented soyfoods and stomach cancer. Our analysis shows, in agreement with the conclusions of Messina *et al.* (3), that the “crude” (unadjusted) data suggest that high intake of fermented soyfoods increases the risk of stomach cancer, whereas high intake of nonfermented soyfoods lowers the risk. However, further analysis shows that fermented and nonfermented soyfoods may be correlated with salt and fruit/vegetable intake, respectively, that are themselves directly associated with stomach cancer risk (12). The respective roles of salt, *N*-nitroso compounds, fruit/vegetable intake, and other dietary factors have not been adjusted for in the majority of the studies on soyfoods. The apparent effects of soy on stomach cancer risk may be simply due to these associations with actual causal factors. Our results emphasize that careful adjustment of potential confounders is critical in the evaluation of the role of soyfoods in the etiology of stomach and other cancers.

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Materials and Methods

Identification of Studies. A computerized search of the MEDLINE English language literature on soyfoods and stomach (or gastric) cancer yielded few relevant publications. We, therefore, searched the reference lists of English language publications of diet and stomach cancer studies that were conducted in Asia or among Asians living in the United States or elsewhere. (Stomach cancer studies that were conducted among non-Asians were not reviewed because soyfoods are rarely consumed in these populations; Ref. 3.) For completeness, we also checked our reference list by conducting a MEDLINE search of English language stomach cancer studies conducted in Asia (*i.e.*, Japan, China, and Korea) or among Asians and published from 1966 through 1999. We identified a total of 6 cohort studies (13, 16, 24, 30, 32, 33) and 14 case-control studies (14, 15, 17–23, 25, 26, 28, 29, 31) in which individual data on intake of soyfoods were available and risk estimates and CIs³ were presented or could be calculated. For the Japanese cohort study of Hirayama (12), we included the results from a 1990 update of the findings (13). Intake of fermented soyfoods was investigated in 5 (13, 16, 20, 32, 33) of the cohort studies and 10 (15, 17–19, 23, 25, 26, 28, 29, 31) of the case-control studies (Table 1), whereas intake of nonfermented soyfoods was investigated in 2 of the cohort (16, 24) and 9 (14, 15, 17, 18, 20–23, 26) of the case-control studies (Table 2). Relevant information regarding each of the studies [*i.e.*, study design, sample size (*i.e.*, number of cases and controls, if applicable), years of follow-up or study, source of the cohort or cases and controls, and percentage of histologically confirmed stomach cancers] is shown (Tables 1 and 2). With the exception of three case-control studies that were population based (20–22), the studies were hospital based with other hospital patients as the control group. However, two hospital-based case-control studies included a population-based group, as well as a hospital control group (17, 28). The extent of histological confirmation of stomach cancer was not provided for the cohort studies, including one conducted in Korea (24) or two conducted in Japan in which stomach cancer deaths were identified from death certificates (13, 30). For three other cohort studies [one in Japan (33) and two among Japanese-Americans (16, 32)], the extent of histological confirmation is likely to be high because incident stomach cancers were identified by linkage with the tumor registries covering these study areas. Among the case-control studies, the percentage of histologically confirmed stomach cancer was 100% or nearly 100% in eight studies (14, 17–19, 22, 23, 26, 29), 52–88% in three studies (20, 21, 28), and was not specified in three other studies (15, 25, 31).

In all of the studies, soy intake was part of a broader dietary assessment, and the relation between soy intake and stomach cancer had not been a prior hypothesis. Although the specific definitions of high and low soy intake varied from study to study, RRs of stomach cancer by categories of soy intake, with adjustment for age and sex (in most studies) were reported (Tables 1 and 2).

Statistical Analysis. In our meta-analysis, we examined separately the influence of fermented (miso, fermented soybeans, and soybean paste; Table 1) and nonfermented (tofu, soymilk, and processed tofu products) soyfoods (Table 2) on the risk of stomach cancer. For the pooled analysis, we took the reported point estimate and SE of the log OR/RR (calculated from

results presented in the report or obtained from investigators, such as 95% CIs) associated with the highest *versus* the lowest level of soy intake for each study. A pooled estimate was calculated using a fixed effects model in which the effect measures are log ORs/RRs weighted by the inverse of the variance of the log OR/RR, giving larger studies greater weight in the summary measure. All reported *P*s were derived from two-sided statistical tests.

Results

Results on the association between fermented soyfoods and risks of stomach cancer are shown, separately for cohort and case-control studies (the studies are ordered by increasing magnitude of the OR/RR; Table 1). Three studies (13, 28, 29) found that high (at least daily) intake of miso was associated with a lower risk of stomach cancer (ORs/RRs ranged from 0.58–0.86); the result was statistically significant in one study (13). In four other studies (16, 18, 29, 30), risk of stomach cancer was weakly or not associated with intake of miso (ORs/RRs were between 0.90 and 1.04). However, in 10 other studies, high intake of fermented soyfoods was associated with an increased risk of stomach cancer; ORs/RRs ranged from 1.2–10.3. The increased risk was statistically significant in six of the studies (17, 19, 23, 25, 26, 31). When we included all 15 studies in a meta-analysis, the pooled OR/RR for high intake of miso was 0.90 (95% CI, 0.86–0.94). This apparent inverse association was mainly due to the reduced risk observed in the very large cohort study of Hirayama (13) that included over 5200 stomach cancers (or some 65% of the cancers included in the pooled analysis). When we excluded results from this one study, the pooled estimate based on the other 14 studies was 1.26 (95% CI, 1.11–1.43). When we further excluded the other most extreme study [*i.e.*, the study by Crane *et al.* (25), which found a 10-fold increased risk associated with high soybean paste intake], the pooled estimate was reduced slightly (OR/RR, 1.21; 95% CI, 1.07–1.38), but it remained statistically significant. We also calculated a pooled estimate of risk separately for cohort and case-control studies. The pooled estimate was 1.13 (95% CI, 0.85–1.49) for cohort studies [Refs. 16, 30, 32, and 33; excluding Hirayama (13)] and 1.30 (95% CI, 1.13–1.50) for case-control studies (15, 17–19, 23, 25, 26, 28, 29, 31).

Table 2 summarizes the studies with data on nonfermented soyfoods and risk of stomach cancer, separately for cohort and case-control studies (the studies are ordered by decreasing magnitude of the OR/RR). One study showed an increased risk of stomach cancer in association with high tofu intake (15), and another showed no association between intake of soybean milk and risk (23). A reduced risk ranging from 0.2–0.89 was found in the other 10 studies; results were statistically significant in 4 of these (20–22, 26). When we conducted a meta-analysis, the OR/RR for high intake of nonfermented soyfood was 0.72 [95% CI, 0.63–0.82; the OR of 0.69 found by Haenszel *et al.* (14) was not included in this meta-analysis because a SE was not presented in the report and could not be calculated]. A reduced risk was observed for both cohort and case-control studies; the pooled estimate was 0.61 (95% CI, 0.38–0.98) for the cohort studies (16, 24) and 0.73 (95% CI, 0.63–0.83) for the case-control studies (15, 17, 18, 20–23, 26).

Because miso and other fermented soyfoods may be a marker of salt intake and nonfermented soyfoods may be a marker of plant food intake, we also examined the risks associated with intake of salt and plant food in the same studies reviewed in Tables 1 and 2. Fig. 1 shows graphically the

³ The abbreviations used are: CI, confidence interval; OR, odds ratio; RR, relative risk.

Table 1 Intake of fermented soyfoods and risk of stomach cancer in C^a and CC studies

Study (Ref.) area; yr of enrollment/recruitment	No. of subjects ^a /yr of FU (C)/% HC	C population or sources of cases/controls	Factors controlled for in analysis on soyfood	Frequency of intake of fermented soyfood	OR/RR (95% CI) ^b for fermented soyfood	Frequency of intake of salted foods	OR/RR (95% CI) ^b for salted foods
C studies							
Hirayama (13) Japan 1966	5247 ca, 17 yr %HC-DK, death certificates	29 health center districts	Age, sex	1+/d vs. nondaily miso	0.86 (0.82–0.90)	No data	No data
Nomura (16) Hawaii 1985	150 ca, 19 yr %HC-DK, linkage to Hawaii Tumor Registry	Japanese men in Hawaii	Age	5+/wk vs. ≤1/wk miso	0.90 (0.50–1.30)	Always vs. never/seldom; table salt/soy sauce	1.0 (0.6–1.6)
Kato (30) Japan 1985	57 ca, 6 yr %HC-DK, death certificates	Male and female inhabitants of 1 county near Aichi prefecture	Age, sex	2+cup/d vs. <1 cup/d miso	1.04 (0.48–2.25)	No data	No data
Galanis (32) Hawaii 1975–80	64 ca, 15 yr (M) %HC-DK, linkage to Hawaii Tumor Registry	Random cohort of Japanese residents in Hawaii	Age, education, birthplace, smoking, alcohol	1+/wk vs. none miso	1.2 (0.7–2.0)	4+/wk vs. none high salt food	0.9 (0.5–1.8)
Galanis (32) Hawaii 1975–80	44 ca, 15 yr (F) %HC-DK, linkage to Hawaii Tumor Registry	As above	Age, education, birthplace	1+/wk vs. none miso	1.3 (0.7–2.4)	4+/wk vs. none high salt food	1.5 (0.6–3.4)
Inoue (33) Japan 1985–89	69 ca, 6 yr %HC-DK, 87% were identified from hospital records/registry	5373 subjects who underwent gastroscopy at Aichi Cancer Center	Age, sex	1+/d vs. rare miso	2.49 (0.6–10.3)	≥2–3×/wk vs. rare salted fish gut	1.3 (0.7–2.4)
CC studies							
Kono (28) Saga Prefecture, Japan 1979–82	139/2852 (2574 hospital, 278 population controls), 88% HC	Cases diagnosed at a stomach cancer referral center; hospital/population controls	Age, sex	1+/d vs. <1/mo miso	0.58 (0.26–1.29) ^c	1+/d vs. <1/mo salty foods	1.1 (0.7–1.8)
Kato (29) Japan 1985–1989	135/1767 (F) 100% HC	Aichi Cancer Center-controls were free of stomach cancer or gastritis	Age, residence	Daily vs. <1/mo miso	0.83 (0.44–1.58)	≥2–3/wk vs. less salted fish gut	0.5 (0.3–1.0)
Inoue (18) Nagoya, Japan 1988–1991	668/668 100% HC	Aichi Cancer Center, hospital control	Sex	3–4+/wk vs. less miso	0.95 (0.75–1.20)	3–4+/wk vs. less salty food	1.04 (0.8–1.3)
Kato (29) Japan 1985–1989	283/1247 (M) 100% HC	See above	Age, residence	Daily vs. <1/mo miso	1.04 (0.60–1.81)	≥2–3/wk vs. less salted fish gut	1.5 (1.1–2.1)
Tajima (15) Japan 1981–1983	93/186 %HC-DK, based on clinical and histology	Aichi Cancer Center, hospital controls	Age, sex	1+/d vs. <daily miso	1.31 (0.7–2.3)	Liked salty foods	2.60
Hu (19) China 1985–1986	221/241 100% HC	2 main hospitals in Harbin, hospital controls	Not specified	>5.5 gm/d vs. less fermented soybean	1.51 (1.02–2.23)	No data	No data
Hirohata (31) Japan	260/520 %HC-DK	Sources of cases not specified, hospital controls	Age, occupation	High vs. low miso	1.60 (1.00–2.60)	High vs. low salted fish	1.9 (1.2–3.1)
Lee (23) Taiwan	210/810 100% HC	4 main hospitals in Taipei, hospital controls	Not specified	11+/wk vs. 2/wk fermented soybean	1.73 (1.09–2.74)	6+/mo vs. <1/mo salted meats	2.9 (1.8–4.7)
Hoshiyama (17), Saitama Prefecture, Japan	294/483 100% HC	1 prefecture, same number of hospital/population controls	Age, sex, smoking, other dietary factors	2+/d vs. <1/d miso	2.00 (1.2–3.5) ^d	High vs. low salted fish	2.3 (1.5–3.4)
Lee (26) Korea 1990–1991	213/213 100% HC	2 teaching hospitals in Seoul, hospital controls	Age, sex, education, social class, residence, dietary factors	2–3+/wk vs. <1/mo salted soybean paste	5.50 (2.5–12.1)	High vs. low salt preference	3.7 (1.1–12.5)
Crane (25) Korea 1962–68	170/170 %HC-DK, based on clinical/histology	Mission hospital in southwest Korea, hospital controls	Not specified	>200 gm vs. less salted soybean paste	10.29 (4.07–26.05)	20+ gm vs. none soy sauce	6.9 (4.0–12.1)

^a Number of cases for C (cohort) studies; number of cases and controls for CC (case-control) studies; FU, follow-up; %HC, percentage histologically confirmed; DK, don't know; M, males; F, females; ca, cases.

^b OR/RR presented compared highest versus lowest level of intake of specific food of interest shown in the previous column.

^c Results using hospital controls as this represented over 90% of the comparison group.

^d Results using population controls as the comparison group.

Table 2 Intake of nonfermented soyfoods and risk of stomach cancer

Study (Ref.) area	No. of subjects ^a / yr of FU (C)/ % HC	Cohort population or sources of cases/ controls	Factors controlled for in analysis on soyfood	Frequency of nonfermented soyfood intake	OR/RR (95% CI) ^b for soy food	Frequency of vegetable/fruit intake	OR/RR (95% CI) ^b for vegetable/fruit
C studies							
Nomura (16) Hawaii 1985	150 ca, 19 yr %HC-DK, linkage to Hawaii Tumor Registry	Japanese men in Hawaii	Age	5+/wk vs. ≤1/wk tofu	0.7 (0.2–2.3)	≥5/wk vs. ≤1/wk all fruits	0.8 (0.5–1.3)
Ahn (24) Korea DK yr of enrollment	Not available, 3 yr %HC-DK	Cohort of 14,533 males ages 40–44	Not specified	Highest vs. lowest quartile tofu	0.60 (0.40–1.10)	Not data	Not data
CC studies							
Tajima (15) Japan 1981–1983	93/186 %HC- DK, based on clinical or histology	Aichi Cancer Center, hospital controls	Age, sex	4+/wk vs. <1/wk bean curd	1.46 (0.77–2.74)	4+/wk vs. <1/wk specific vegetables	1.2–2.5
Lee (23) Taiwan; DK yr of recruitment	213/213 100% HC	4 main hospitals in Taipei; hospital controls	Not specified	11+/wk vs. 2/wk bean milk ^c	1.05 (0.60–1.83)	15+/wk vs. <14/ wk green vegetables ^c	0.82 (0.52–1.28)
Inoue (18) Nagoya, Japan 1988–1991	668/668 100% HC	Aichi Cancer Center; hospital controls	Sex	3–4+/wk vs. less bean curd	0.89 (0.71–1.11)	3–4+/wk vs. less green vegetables	0.93 (0.75–1.17)
Ji (20) China 1988–1989	354/632 (F) 52% HC	10 urban districts of Shanghai; population controls	Age, income, education	23.4+/mo vs. ≤5.5/mo- all soybean products ^d	0.80 (0.40–1.10)	≥263.5/mo vs. ≤158.9/mo all vegetables	0.7 (0.5–1.1)
Haenszel (14) Japanese in Hawaii, mid 1960s	220/440 96% HC	Main hospitals in Oahu, Hawaii; hospital controls	Not specified	Above vs. below average frequency bean curd	0.69	Above vs. below average frequency raw vegetables	OR ranged between 0.4 and 0.6 for most vegetables
Hoshiyama (17), Saitama Prefecture, Japan 1984–1990	294/483 100% HC	1 cancer center hospital; hospital and population controls	Age, sex, smoking, dietary factors	8+/wk vs. ≤4/wk soybean products excluding miso	0.6 (0.4–1.1) ^e	6+/wk vs. ≤1/wk raw vegetables	0.4 (0.2–0.7)
You (21) China 1985–86	564/1131 55% HC	County/commune hospitals in Linqu and Yidu County; population controls	Sex, age, family income	>5.5 gm/d vs. ≤2.7 gm/d soybean	0.6 (0.4–0.8)	>427 gm/d vs. ≤200 gm/d- total vegetables	0.4 (0.3–0.6)
Ji (20) China 1988–1989	819/632 (M) 52% HC	10 urban districts of Shanghai, population controls	Age, income, education, smoking and alcohol	23.4+/mo vs. ≤5.5/mo all soybean products ^d	0.50 (0.40–0.70)	≥263.5/mo vs. ≤158.9/mo- all vegetables	0.4 (0.3–0.5)
Lee (26) Korea 1990–1991	213/213 100% HC	2 teaching hospitals in Seoul, hospital controls	Age, sex, education, economic status, residence, dietary factors	2–3+/wk vs. none dubu (tofu, soybean curd)	0.2 (0.10–0.80)	2–3+/wk vs. none cabbage	0.2 (0.02–0.3)
Gao (22) China 1995	153/234 100% HC	Yangzhong Cancer Registry, population controls	Age, sex	3+/wk vs. <1/wk soybean products	0.2 (0.04–1.0)	Frequent vs. almost never raw vegetables	0.07 (.04–0.13)

^a Number of cases for C (cohort) studies; number of cases and controls for CC (case-control) studies; FU, follow-up; %HC, percentage histologically confirmed; DK, don't know; M, males; F, females; ca, cases.

^b OR/RR presented compared highest vs. lowest level of intake of specific food of interest shown in the previous column.

^c Intake before age 20 years.

^d Included soybean milk, bean curd, fried bean curd, and other bean products.

^e Results using population controls as the comparison group.

ORs/RRs associated with intake of fermented soyfoods (*left*) and salty foods (*right*); these ORs/RRs were unadjusted for each other. The *last two columns* of Table 1 show for each study the specific salty food investigated, definition of high and low levels of intake, and the corresponding risk estimate comparing a high *versus* low level of intake.

The results in Fig. 1 and Table 1 show that the risks for stomach cancer associated with high intake of salt and miso

generally follow a similar pattern. Specifically, of the nine studies that found an increased risk in association with high miso intake (OR/RR of 1.2 or greater) and presented results on salt (salty food) intake, eight also found an increased risk (OR/RR ranged from 1.3–12.4) in association with such high salt intake. (The RR was 0.9 for males in one study; Ref. 32). Of the five studies in which high intake of miso was inversely or not associated with an increased risk of stomach cancer

Fig. 1. Left, risk of stomach cancer in association with intake of fermented soyfoods. Right, risk of stomach cancer in association with intake of salt. Each study-specific point estimate is plotted as a circle, and its 95% CI is denoted by a line through the circle.

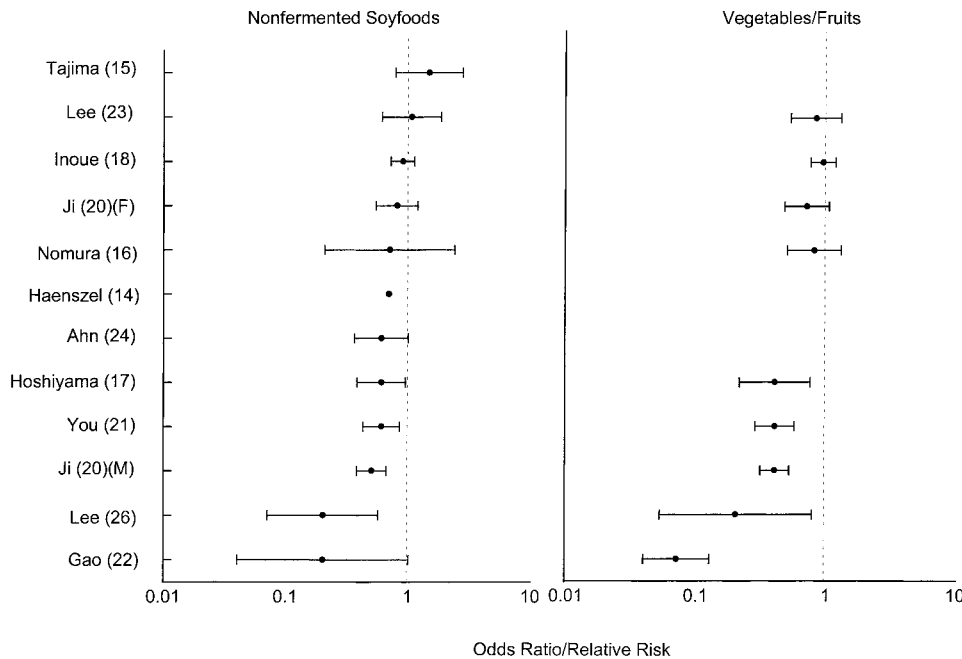
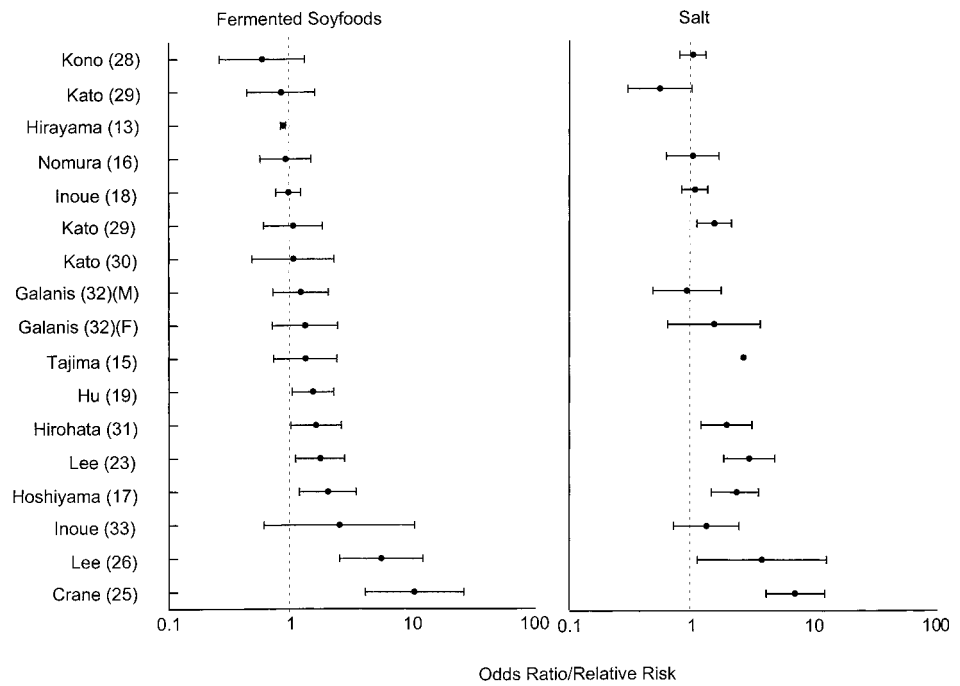


Fig. 2. Left, risk of stomach cancer in association with intake of nonfermented soyfoods. Right, risk of stomach cancer in association with intake of vegetables/fruits. Each study-specific point estimate is plotted as a circle, and its 95% CI is denoted by a line through the circle.

(OR/RR ranged from 0.58–1.04), high intake of salt (salty foods) was associated with an increased risk in one study (males in Ref. 29; OR of 1.5) but not in four others (Refs. 16, 18, 28, and females in Ref. 29; OR/RR of 0.5–1.1). [Three of the studies in Table 1 did not present results associated with salt (salty food) intake (13, 19, 30).]

Fig. 2 shows graphically the ORs/RRs associated with intake of nonfermented soyfoods (left) and vegetable/fruit intake (right); these ORs/RRs were unadjusted for each other. The last two columns of Table 2 show for each study the

specific vegetable/fruit investigated, definition of high versus low levels of intake, and the corresponding risk estimate comparing the high versus the low level of intake.

The results in Fig. 2 and Table 2 show that the risks for stomach cancer associated with high intake of vegetables/fruits and nonfermented soyfoods show remarkably similar patterns. In all of the studies that found an inverse association between intake of nonfermented soyfoods and stomach cancer risk (OR/RR of 0.89 or lower), a reduced risk of stomach cancer was also reported in association with high intake of total veg-

etables (14, 20, 21), specific vegetables (17, 18, 22, 26), or fruits (Ref. 16; Table 2). Of the two studies that found no association between intake of nonfermented soyfoods and stomach cancer risk, one found a reduced risk (23) and the other an increased risk in association with high intake of vegetables (15).

Discussion

Before discussing these results, it is important to note that these studies were not designed primarily to investigate the role of soyfoods. They were conducted to identify dietary and nondietary determinants of stomach cancer in select high-risk populations in Asia. Although soyfoods were among the specific food items assessed, few of the investigators specifically described or discussed their findings on soy intake in relation to stomach cancer risk. In the majority of studies, only age and sex (if applicable) were adjusted for in the analyses on soyfoods (see below). The specific soyfoods that were included varied, depending largely on the Asian ethnic group/country of the study. For example, most of the data on fermented soyfoods were based on studies conducted in Japan or among Japanese-Americans (Table 1). All but 1 (14) of the 11 studies conducted in Japan or among Japanese in Hawaii asked about intake of miso, whereas only 4 of these studies also asked about intake of tofu (15–18). Of the five studies conducted among Chinese living in China or Taiwan, one asked about fermented soybeans (19), three asked about all soybean products combined (20–22), and one asked separate questions regarding intake of soybean milk and fermented beans (23). Of the three studies conducted in Korea, one asked about tofu (24), one about soybean paste (25), and one about intake of soybean paste and tofu (26).

Reasons for the finding of an inverse association between high miso intake and risk in the Japanese cohort study of Hirayama (13), but an increased risk in most of the other cohort and case-control studies, are not apparent. Because of the divergent results and the large contribution of this single study to the pooled results, we conducted pooled analyses with and without the Hirayama (13) study.

Our pooled results suggest that soyfood may differentially affect the risk of stomach cancer, depending on whether it is fermented or nonfermented soyfood. Risk of stomach cancer decreased significantly in association with high intake of nonfermented soyfoods (including tofu, soybeans, and soy milk). However, high intake of fermented soyfoods (miso, fermented soybeans, and soybean paste) was associated with a statistically significant increased risk when we excluded the Hirayama study (13). This result was reversed, and the pooled result suggested a decreased risk when the Hirayama study (13) was retained in the analysis.

Because fermented and nonfermented soyfoods may be markers of other dietary factors that influence risk of stomach cancer, we explored whether the presence of potential dietary confounders may explain the observed results relating to fermented and nonfermented soyfoods. We specifically investigated the role of salt and plant foods because they have been shown to influence stomach cancer risk and because risk estimates associated with these two groups of foods were available in most of the studies included in this meta-analysis (*last column* of Tables 1 and 2). However, salt and plant foods are only examples of potential dietary confounders in studies of fermented and nonfermented soyfoods. Besides salt, other compounds such as *N*-nitroso compounds may also contribute to the observed association

between fermented soy products and stomach cancer. Nine studies presented any data on intake of *N*-nitroso compounds: nitrate-containing foods (32), broiled fish (15, 25, 26, 28, 30), smoked foods (17, 23), and ham/bacon/sausage (16) were asked. Although there was some concordance between the ORs/RRs for foods rich in *N*-nitroso compounds and fermented soyfoods, the data are too few to be confident that such a relationship exists.

Our results do suggest concordance in the results between fermented soyfoods and salt (Table 1 and Fig. 1) and between nonfermented soyfoods and plant foods (Table 2 and Fig. 2), pointing to the importance of considering these and other potential confounders (such as *N*-nitroso compounds) in future studies. The results on salt intake and stomach cancer are not totally consistent in the studies included here; this is not surprising because of the well-recognized difficulty in assessing total salt intake (32). More importantly, the assessment of salt intake varied in this group of studies; all salty foods combined, specific high-salt food(s), salt, soy sauce, or salt preference were investigated in the different studies. (Note that soy sauce is low in isoflavone content; Ref. 34.)

Of the studies reviewed, one investigated the joint associations of salt and soybean paste (26). An increased risk of stomach cancer associated with high intake of soybean paste stew was present for those who preferred low, intermediate, or high amounts of table salt in their diet (26). This (26) and another study (17) also offered some information on the association of fermented and nonfermented soyfoods in univariate and multivariate analyses when the two types of soyfoods and other dietary factors were considered simultaneously. In one study, the risk reduction associated with tofu intake was enhanced (OR was 0.3 in univariate analysis and 0.2 in multivariate analysis), and the increased risk associated with soybean paste was reduced (OR was 10.3 in univariate analysis and 5.5 in multivariate analysis; Ref. 26). In the multivariate analysis that included two soyfoods and seven other dietary factors, the decreased risks associated with vegetable intake (cabbage and spinach) and the increased risk associated with salt preference remained statistically significant (26). A somewhat different picture emerged in another study (17) that examined simultaneously the association of salty foods, miso soup, soybean products (excluding miso), raw vegetables, green-yellow vegetables, and six other dietary factors on risk of stomach cancer. In this study, the OR associated with soybean products changed from 0.6 in a univariate analysis to 0.9 in a multivariate analysis; the respective ORs associated with high intake of fruits, green-yellow vegetables, and raw vegetables were 0.4, 0.5, and 0.4 in univariate analysis and 0.7, 0.8, and 0.5 in multivariate analysis. In contrast, high intake of miso and salty foods were significant risk factors in both univariate (respective ORs were 2.1 and 2.3) and multivariate (respective ORs were 1.9 and 2.2) analyses (17). Thus, in this study, the increased risk associated with high intake of miso remained, whereas the decreased risk associated with high intake of nonfermented soyfoods was largely eliminated after adjustment for each other and other dietary factors including salty foods and vegetable intake. However, it cannot be determined from the multivariate results presented whether this change in OR associated with nonfermented soyfoods is due to the adjustment of miso, salt, a specific plant food, or a combination of these dietary factors (17).

The question remains whether any conclusions can be reached regarding the role of nonfermented and fermented soyfoods in the etiology of stomach cancer. If we accept the

pooled result (excluding the Hirayama study; Ref. 13) that fermented soyfoods increases the risk of stomach cancer, is this observation due to specific soy constituents or to the salt content, *N*-nitroso compounds, or other dietary components of fermented soyfoods? Is there any evidence that the increased risk associated with salt intake (at least in those studies conducted in populations in which soyfoods are consumed) may be confounded by intake of fermented soyfoods such as miso?

Although high intake of miso (17) and soybean paste (26) remained as significant risk factors when salt intake was considered in the two studies discussed above, additional data are needed to determine with certainty that high salt (or other dietary components) in fermented soyfoods is not the apparent explanation. We are not aware of specific soy constituents in fermented soyfoods that may have harmful effects on the gastric mucosa. Future studies need to better characterize not only intake of total salt and *N*-nitroso compounds, but also the contribution of fermented soyfoods to their total intake. With the availability of more precise information on these exposure variables, the separate and combined effects of fermented soyfoods, salt, and *N*-nitroso compounds on stomach cancer risk can be determined.

If we accept at face value the pooled result that high intake of nonfermented soyfoods decreases the risk of stomach cancer, is this observation due to the high intake of vegetables/fruits, specific antioxidants, or are there specific soy constituents in nonfermented soyfoods that may protect the gastric mucosa? Is there any reason to believe that the inverse association with high intake of vegetables/fruits may be "explained" by the associations of nonfermented soyfoods, at least in those populations in which soyfoods are consumed?

Various constituents of soyfoods (*e.g.*, protease inhibitors, saponins, and isoflavones) may, in fact, lower the risk of stomach cancer (3). The reduced risk associated with intake of nonfermented soyfoods remained in one study (26) but was largely eliminated in another (17) after adjustment for intake of fermented soyfoods, salt, and vegetables. More data are needed to firmly establish the role, if any, of nonfermented soyfoods and stomach cancer risk. It is important that future studies obtain information on intake of different types of nonfermented soyfoods so that analyses may be conducted by individual soyfoods (*e.g.*, tofu, and soymilk) and for all nonfermented soyfoods combined. Results from both studies (17, 26) suggest that it is unlikely that the inverse association with intake of fruits/vegetables may be explained by high intake of nonfermented soyfoods. Moreover, a decreased risk of stomach cancer in relation to high intake of fruits/vegetables has been reported in a large number of stomach cancer studies (primarily case-control design) conducted in both high- and low-risk populations worldwide.

In summary, the role of soyfoods in stomach cancer cannot be determined until the roles of potential confounders including intake of salt, *N*-nitroso compounds, plant foods, and other dietary factors are considered. Few of the published studies examined the independent effect of intake of fermented or nonfermented soyfoods after adjustment for other relevant dietary factors; this is clearly needed.

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