Meta-analysis of Soy Consumption and Gastrointestinal Cancer Risk

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Soy consumption has received considerable attention for its potential role in reducing cancer incidence and mortality. However, its effects on gastrointestinal (GI) cancer are controversial. Therefore, we performed a meta-analysis to evaluate the association between soy consumption and gastrointestinal cancer risk by searching for prospective studies in PubMed, Web of Science, EMBASE and the reference lists of the included articles. The study-specific odds ratio (OR), relative risk (RR) or hazard ratio (HR) estimates and 95% confidence intervals (CIs) were pooled using either a fixed-effect or random-effect model. Twenty-two independent prospective studies were eligible for our meta-analysis, including 21 cohort studies and one nested case-control study. Soy product consumption was inversely associated with the incidence of overall GI cancer (0.857; 95% CI: 0.766, 0.959) and the gastric cancer subgroup (0.847; 95% CI: 0.722, 0.994) but not the colorectal cancer subgroup. After stratifying the results according to gender, an inverse association was observed between soy product intake and the incidence of GI cancer for females (0.711; 95% CI: 0.506, 0.999) but not for males.

In recent years, soy consumption has received considerable attention for its potential role in reducing the incidence and mortality of cancer1–3. Much literature has studied the possible association between soy consumption and gastrointestinal (GI) cancer4–6. The lower risk of GI cancer that results from a greater soy intake may be explained through multiple biological effects, including inflammation inhibition, antioxidant activity, anti-proliferative properties and angiogenesis9–11.

However, population studies of the association between soy intake and GI cancer risk have yielded inconsistent results. In 2016, Umesawa et al. reported that the consumption of large quantities of miso soup was associated with an increased risk of gastric cancer among the Japanese population12. In 2015, Wada et al. reported that the higher intake of soy foods was significantly associated with a lower risk of stomach cancer6. Some recent meta-analyses reported that the consumption of soy was inversely associated with gastric cancer13, 14, while in 2016, Tse et al. reported that there was no association between soy intake and gastric cancer15.

Previous meta-analysis studies on this topic combined both retrospective case-control studies and prospective cohort studies. To overcome the shortcomings of the retrospective studies, such as the likelihood of exposure to recall bias and selection bias, we investigated the association between soy intake and GI cancer only in prospective studies.

Results

Literature search. The literature search through PubMed, Web of Science and EMBASE identified a total of 452 abstracts. After removing duplicates, 396 abstracts remained. The title and abstract screening excluded 358 articles. Thus, we identified 38 potentially relevant studies. The entire text of all remaining studies was reviewed, and 15 studies were excluded for the following reasons: five studies did not report the association between the intake of soy food or its subtypes and gastrointestinal cancer risk7, 16–19, one study reported serum concentrations of isoflavone but not dietary intake8, one study's cohort source was hospital-based20, one study was a duplicate report on the same study population that Galanis et al.(1998) used21, and eight studies were either reviews or systematic reviews14, 15, 22–27. Therefore, twenty-two independent prospective studies were eligible for our meta-analysis, including 21 cohort studies6, 12, 28–46 and one nested case-control study47. The flow diagram of our systematic literature search is shown in Fig. 1.

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Study characteristics. The characteristics of the eligible studies are outlined in Table 1. We included 22 independent studies that contained a total of 12,901 cancer cases from 965,466 participants. Fifteen studies reported the association between soy consumption and gastrointestinal cancer incidence, while seven studies reported the association between soy consumption and gastrointestinal cancer mortality. Of the 22 prospective studies, twenty-one were cohort studies and one was a nested case-control study.

Among the 22 studies, Wada et al., Oba et al., and Nagata et al. reported on the gastric cancer incidence, colon cancer incidence and gastric cancer mortality, respectively, of the same study cohort. The studies by Kweon et al., Yang et al., and Akhter et al. were based on the Shanghai health study cohort (China) and reported on the gastric cancer incidence and colorectal cancer incidence, respectively. Hara et al. and Akhter et al. reported the gastric cancer incidence and colorectal cancer incidence, respectively, of the Japan Public Health Center cohort. Umesawa et al., and Tokui et al. focused on the Japan Collaborative cohort. Although Iso et al. and Tokui et al. reported on the gastric cancer mortality of this cohort, Tokui et al. studied different exposure factors.

The included studies were published from 1990–2016. Among these studies, thirteen were conducted in Japan, two were conducted in the U.S., one was conducted in Korea, one was conducted in Sweden, one was conducted in China, one was conducted in Singapore and one was conducted at a multicenter in Europe. Thirteen of the included studies reported the outcomes of stomach cancer, seven studies reported the outcomes of colorectal cancer and two studies reported the outcomes of both stomach cancer and colorectal cancer.

All studies reported the association between soy intake and the incidence of mortality from gastrointestinal cancer. The Food Frequency Questionnaire (FFQ) was designed to assess the consumption of the specific food type used in each study independently. The reproducibility of the FFQs from thirteen of the studies was independently validated against previously reported studies. All studies clearly categorized several foods under the soy
| Reference | Location | Cancer type | Study years | Age | Cancer Size/ Cohort Size | Intake measurements | Validity of FFQ | Soy consumption assessed | Cancer & death ascertainment |
|-----------|----------|-------------|-------------|-----|-------------------------|---------------------|------------------|-------------------------|-----------------------------|
| Umesawa12 | Japan    | Gastric cancer | 1988–2009  | 40–79 | 787/40, 729             | Self-administered FFQ | Yes             | Miso soup               | Population-based cancer registries; systematic review of death certificates |
| Hedelin42  | Sweden   | Colorectal cancer | 1991–2010 | 30–49 | Female: 206/48, 268     | Self-administered FFQ | No              | Isoflavonoids           | Swedish cancer registry; total population register |
| Wada6     | Japan    | Gastric cancer | 1992–2008  | ≥35  | Male: 441/14, 219 Female: 237/16, 573 | Self-administered FFQ | Yes             | Miso soup, tofu (soy bean curd), deep-fried tofu, freeze-dried tofu, natto, houba-miso, soymilk, and boiled soy beans. | Regional population-based cancer registries; death certificate-only registration |
| Ko11      | Korea    | Gastric cancer | 1993–2008  | ≥35  | 166/9724                 | Self-administered FFQ | No              | Soybean/tofu, soybean pasta (miso soup) | Korean Central Cancer Registry; National Death Certificate databases |
| Kweon46   | China    | Gastric cancer | M: 2002–2006 F: 1996–2004 | M:40–74 F: 40–70 | Male: 324/61, 482 Female: 354/74, 941 | In-person interview | Yes             | Soy milk, Tofu, dry bean, fresh bean, bean sprout | Shanghai cancer registry; death certificate registries and confirmation through home visit |
| Hara40    | Japan    | Gastric cancer | 1995–2006  | 45–74 | Male: 899/39,569 F: 350/45, 312 | Self-administered FFQ | Yes             | Miso soup, soymilk, tofu for miso soup, tofu for other dishes, yushidofu (predrained tofu), koyadofu (freeze-dried tofu), aburaage (deep-fried tofu), and natto (fermented soybeans) | Population-based cancer registries; |
| Yang39    | China    | Colorectal cancer | 1997–2005 | 40–70 | Female: 321/68, 412     | In-person interview | Yes             | Soy milk, tofu, fried tofu, dried or pressed tofu, fresh green soy beans, dry soy beans, soy sprouts, and other soy products | Population-based Shanghai Cancer Registry; Shanghai Municipal Center for Disease Control and Prevention |
| Wang38    | USA      | Colorectal cancer | 1992–2005 | ≥45  | Female: 3234/38, 408    | Self-administered semi-quantitative FFQ | Yes             | Tofu | Medical record review; death certificates |
| Butler37  | Singapore Chinese | Colorectal cancer | 1993–2005 | 45–74 | Total: 961/61, 321     | Self-administered Quantitative FFQ + Interview | Yes             | Tofu in soups mixed dishes or alone, other tau bea, foojook vegetarian meats, yong tau foo, other tau pok in soups | Population-based Singapore Cancer Registry; Singapore Registry of Births and Deaths |
| Akhter36  | Japan    | Colorectal cancer | 1995–2004 | 45–74 | Total: 886/83, 063      | Self-administered FFQ | Yes             | Miso soup, tofu (soybean curd) for miso soup, tofu (boiled or cold) for other dishes, yushidofu (predrained tofu), koyadofu or shimitofu (freeze-dried tofu), aburaage (deep-fried tofu), natto (fermented soybean), and soymilk (soybean as major ingredient). | Population-based cancer registries; |

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product group, except for those by Ward et al.\(^47\) and Hedelin et al.\(^42\), which only reported the intake of isoflavones (Table 2). Isoflavones are phytoestrogenic compounds that are abundant in soybeans. Eight studies discussed the association between the intake of isoflavones and risk of GI cancer. Miso soup was the most frequently reported

| Reference | Location | Cancer type | Study years | Age | Cancer Size/ Cohort Size | Intake measurements | Validity of FFQ | Soy consumption assessed | Cancer & death ascertainment |
|-----------|----------|-------------|-------------|-----|-------------------------|---------------------|-----------------|-------------------------|----------------------------|
| Oba\(^35\) | Japan    | Colon cancer | 1992–2000   | ≥35 | Male: 111/13,894 Female: 102/16, 327 | Self-administered FFQ | Yes            | Tofu, miso, soybeans, natto, soymilk, okara, dried tofu, fried tofu, deep-fried tofu, and fried tofu with minced vegetables/ seaweed | Regional population-based cancer registries; death certificate-only registration |
| Sauvager\(^40\) | Japan    | Gastric cancer | 1980–1999   | 34–98 | 1270/38, 576 | Self-administered FFQ | Yes            | Tofu (soybean curd), miso soup (soup made of a fermented and cooked soybeans paste) | Hospital records, physician notification and pathology records; Japanese family registration system |
| Galanis\(^28\) | Hawaii, USA, | Gastric cancer | 1975–1994   | ≥18 | Male: 64/5, 610 Female: 44/6, 297 | Interview FFQ | No            | Miso soup | Hawaii Tumor Registry |
| Inoue 1996 | Japan    | Gastric cancer | 1985–1995   | NA | 69/5, 373 | Self-administered FFQ | No            | Soybean-paste soup (miso soup) | Aichi prefectural cancer registry and death certificates |
| Ward\(^47\) (NCC) | European | Colorectal cancer | 1993–2006   | 40–79 | Male: 125/505 Female: 96/381 | Self-administered healthy and lifestyle questionnaire | No            | Isoflavones | Ease Anglia Cancer Registry |

Table 1. Study features of soy consumption and gastrointestinal cancer risk. FFQ: Food Frequency Questionnaire; NA: Not Available.

product group, except for those by Ward et al.\(^47\) and Hedelin et al.\(^42\), which only reported the intake of isoflavones (Table 2). Isoflavones are phytoestrogenic compounds that are abundant in soybeans. Eight studies discussed the association between the intake of isoflavones and risk of GI cancer. Miso soup was the most frequently reported
## Reference Cancer type Exposure RR, HR (95% CI) Adjustments

| Reference | Cancer type | Exposure | RR, HR (95% CI) | Adjustments |
|-----------|-------------|----------|-----------------|-------------|
| Incidence |             |          |                 |             |
| Umesawa12 | Gastric cancer | Miso soup | Both genders 1.66 (1.13–2.45) | Age, sex, body mass index, ethanol intake, smoking status, family history of gastric cancer, walking time, educational status, and area of residence |
| Hedelin42 | Colorectal cancer | Isoflavone | Female 1.06 (0.68, 1.65) | Age, total energy intake, BMI, years of education, smoking status, physical activity, and dietary intake of processed meat, alcohol, and gender |
| Wada4 | Gastric cancer | Soy product | Male 0.71 (0.53–0.96) | Male: age, body mass index, physical activity score, smoking status, alcohol consumption, salt intake and education years |
| Wada4 | Gastric cancer | Soy product | Female 0.58 (0.36–0.94) | Female: age, body mass index, physical activity score, smoking status, alcohol consumption, salt intake, education years and menopausal status |
| Ko41 | Gastric cancer | Isoflavone | Male 0.81 (0.60–1.09) | Age, BMI, metabolic equivalents hours per week per year, chronic gastritis history, family gastric cancer history, born in urban Shanghai, family income, ever drink, ever smoke, and smoking amounts at baseline examinations as well as for median intakes of total calories, red meat, vegetables, sodium, fruit (excluding citrus) |
| Ko41 | Gastric cancer | Isolevans | Male 0.81 (0.60–1.09) | Female 0.60 (0.37–0.98) |
| Kweon46 | Gastric cancer | Soy product | Both genders 1.06 (0.93–1.21) | Age, sex, cigarette smoking, body mass index, alcohol drinking, and area of residence |
| Kweon46 | Gastric cancer | Soy product | Male 1.02 (0.82, 1.25) | Male 0.64 (0.42, 0.99) |
| Kweon46 | Gastric cancer | Soy product | Female 0.99 (0.71, 1.38) | Female 0.57 (0.33, 0.95) |
| Hara46 | Gastric cancer | Soy product | Male 1.07 (0.77, 1.50) | Male 1.84 (1.39, 2.44) |
| Hara46 | Gastric cancer | Soy product | Female 0.71 (0.50, 1.01) | Female 1.17 (0.94, 1.47) |
| Yang39 | Colorectal cancer | Soy product | Female 0.76 (0.56, 1.01) | Age, education, household income, physical activity, BMI, family history of colorectal cancer, total calorie intake, and average intakes of fruit, vegetables, red meat, non-soy calcium, non-soy fiber, and non-soy folic acid and was stratified by birth year. |
| Yang39 | Colorectal cancer | Isoflavones | Female 0.67 (0.49, 0.90) | Female 0.76 (0.56, 1.01) |
| Wang38 | Colorectal cancer | Soy product | Female 0.54 (0.20, 1.46) | Age; race; total energy intake; randomized treatment assignment; smoking; alcohol use, physical activity; postmenopausal status; |
| Butler37 | Colorectal cancer | Soy product | Both genders 0.95 (0.78–1.16) | Age, sex, dialect group, interview year, diabetes at baseline, smoking history, alcohol intake, education, any weekly physical activity, first-degree relative diagnosed with colorectal cancer, and total daily energy intake. |
| Butler37 | Colorectal cancer | Isoflavones | Both genders 0.95 (0.79–1.13) | Male 1.07 (0.78–1.47) |
| Akhter36 | Colorectal cancer | Soy product | Male 0.89 (0.68–1.17) | Male 0.69 (0.48–0.98) |
| Akhter36 | Colorectal cancer | Soy product | Female 1.04 (0.76–1.42) | Female 1.07 (0.78–1.47) |
| Akhter36 | Colorectal cancer | Soy product | Male 0.89 (0.67–1.17) | Male 0.88 (0.64–1.10) |
| Akhter36 | Colorectal cancer | Soy product | Female 1.03 (0.75–1.43) | Female 1.13 (0.81–1.58) |

**Continued**
| Reference   | Cancer type | Exposure | RR, HR (95% CI) | Adjustments                                                                 |
|-------------|-------------|----------|-----------------|-----------------------------------------------------------------------------|
| Oba35       | Colon cancer| Soy product | Male 1.24 (0.77–2.00) | Age, height, alcohol intake, smoking status, BMI, physical exercise, coffee intake, and use of hormone replacement therapy (women only). |
|             |             |           | Female 0.56 (0.34–0.92) |                                                             |
|             |             | Isoflavones | Male 1.47 (0.90–2.40) |                                                             |
|             |             |           | Female 0.73 (0.44–1.18) |                                                             |
| Sauvager45  | Gastric cancer| Soy product | Both genders 1.01 (0.85–1.20) | Sex-specific age, sex, city, radiation dose, sex-specific smoking habits, and education level |
|             |             | Miso Soup | Both genders 1.01 (0.88–1.16) |                                                             |
| Galanis18   | Gastric cancer| Miso Soup | Both genders 1.2 (0.8–1.8) | Age, years of education, Japanese place of birth, and gender (in combined analyses). Analyses among men were also adjusted for cigarette smoking and alcohol intake status |
|             |             |           | Male 1.2 (0.7–2.0) |                                                             |
|             |             |           | Female 1.3 (0.7–2.4) |                                                             |
| Inoue 1996  | Gastric cancer| Miso Soup | Both genders 3.62 (0.79–16.70) | Age and sex |
|             |             |           | Male 1.2 (0.7–2.0) |                                                             |
|             |             |           | Female 1.3 (0.7–2.4) |                                                             |
| Ward47      | Colorectal cancer| Isoflavones | Male 1.12 (0.88, 1.42) | Age, height, weight, family history of colorectal cancer, smoking status, aspirin use, physical activity, and average daily intake of fat, energy, calcium, fiber, alcohol, and red and processed meats. |
|             |             |           | Female 1.19 (0.92, 1.54) |                                                             |

### Mortality

| Reference   | Cancer type | Exposure | RR, HR (95% CI) | Adjustments                                                                 |
|-------------|-------------|----------|-----------------|-----------------------------------------------------------------------------|
| Iso34       | Gastric cancer| Miso soup | Male 0.96 (0.77–1.20) | Age |
|             |             |           | Female 1.18 (0.89–1.58) |                                                             |
|             | Colon cancer| Miso soup | Male 0.87 (0.58–1.28) |                                                             |
|             |             |           | Female 0.84 (0.58–1.23) |                                                             |
|             | Rectal cancer| Miso soup | Male 0.75 (0.48–1.18) |                                                             |
|             |             |           | Female 1.02 (0.56–1.85) |                                                             |
| Kurosawa33  | Gastric cancer| Soy product | All 0.88 (0.31–2.56) | Age, sex, highly salted food, green and yellow vegetables, beans and bean products, mountain herbs, fruits, and the smoking habit |
| Tokui32     | Gastric cancer| Soy product | Male 1.07 (0.73–1.58) | Age |
|             |             |           | Female 1.41 (0.75–2.64) |                                                             |
| Khan31      | Gastric cancer| Soy product | Male 3.6 (0.5–26.0) | Age, health status, health education, health screening and smoking;                                      |
|             |             |           | Female 1.1 (0.1–8.5) |                                                             |
|             | Colorectal cancer| Soy product | Male 0.2 (0.1–0.8) | Male: age and smoking |
|             |             |           | Female 0.9 (0.1–6.9) |                                                             |
| Ngoan30     | Gastric cancer| Soy product | Both genders 0.4 (0.2–0.9) | Both genders: age, sex, smoking, and other dietary factors (processed meat, liver, cooking oil, sui mono, and pickled food). |
|             |             |           | Male 0.9 (0.4–1.8) |                                                             |
|             |             |           | Female 0.8 (0.3–2.2) |                                                             |
|             | Miso soup   |           | Male 1.7 (0.6–4.5) |                                                             |
| Nagata39    | Gastric cancer| Soy product | Male 0.48 (0.27–0.83) | Age, total energy, smoking status (current, former, and never-smokers) and body mass index at age about 21 years; |
|             |             |           | Female 0.49 (0.21–1.12) |                                                             |
| Kato 1992   | Gastric cancer| Miso soup | Both genders 1.04 (0.48–2.25) | Age and sex |

Table 2. The exposure type specific and gender specific risk estimates of GI cancer and soy consumption. RR: Relative Risk; HR: Hazard Ratio; CI: Confidence Intervals; BMI: Body Mass Index.
Soy consumption and GI cancer incidence. In our meta-analysis, the intake of mixed soy types had no cancer site-specific or gender-specific association with GI cancer incidence. Ten studies focused on the association between soy product intake and incidence of GI cancer. The highest versus the lowest categories of soy product consumption were inversely associated with the incidence of overall GI cancer (0.857; 95% CI: 0.722, 0.994; Heterogeneity: $I^2 = 53.3\%$) for colorectal cancer (Fig. 3). Among the males, no association was observed between mixed soy types and the incidence of colorectal cancer.

Soy consumption and GI cancer mortality. The estimated summary risk for the highest versus the lowest categories of soy consumption showed no association with the mortality of overall GI cancer, mortality of gastric cancer, or mortality of colorectal cancer. After stratifying according to gender, no association was observed for females or males.

Detailed results of the subgroup analysis are summarized in Table 3.
Publication bias and sensitivity analysis. The results of the Begg–Mazumdar test and Egger’s test indicated no evidence of a substantial publication bias for most of the analyses, except for the analysis of soy product consumption and the incidence of GI cancer for both genders. Although this analysis showed a publication bias under Egger’s test, it did not show one under the Begg–Mazumdar or funnel test. We strictly followed our inclusion criteria, and therefore, we determined that the results did not suggest any publication bias.

We applied a sensitivity analysis on our positive meta-analysis results. The overall pooled estimate did not substantially vary with the exclusion of any single study (Figs 4 and 5).

Discussion
We systematically reviewed the existing literature from three main databases and identified 22 prospective epidemiological studies that assessed the association between soy consumption and GI cancer risk. The findings showed that there was no association between soy consumption and GI cancer risk. Cancer site-specific and soy subtype-specific subgroup analyses revealed that the highest versus the lowest categories of soy product consumption were inversely associated with the incidence of overall GI cancer and the gastric cancer subgroup, but not the colorectal cancer subgroup. A gender-specific analysis showed that this protective effect that the soy product has on the incidences of GI cancer and gastric cancer was only observed in females.

Our results did not find any association between soy consumption and colorectal cancer risk, which was consistent with some previous meta-analyses, including Yuan et al.22 and Jin et al.48. However, Tse et al.15, Yu et al.26 and Zhu et al.49 reported that soy consumption had an inverse association with CRC. Although the previous studies were inconsistent, our study included the newly reported articles by Umesawa et al.12 and Hedelin et al.42, both of which reported no association between GI cancer risk and soy consumption. Woo et al. (2013) performed a meta-analysis of the risks of gastric and colorectal cancer with flavonoids intake14. The inclusion of this study showed no association between colorectal cancer risk and flavonoids intake when case-control designed studies were included, while a significant inverse association was detected when case-control designed studies were included. Our meta-analysis included only prospective studies, which minimized the recall bias and selection bias from case-control studies, while most retrospective studies reported a significant inverse association. Thus, our most updated and prospective studies included only a meta-analysis, which was more reliable.

Several mechanisms may account for the inverse association between soy product consumption and the incidence of gastric cancer. Two of the major soy isoflavones are genistein and daidzein, which have anti-inflammatory and antioxidative effects46. Genistein is known to inhibit the growth of H. pylori47 and the
activation of the nuclear factor-kappaB (NF-κB) signaling pathway. The classical activation pathway of NF-κB signaling has been identified in regulating inflammation-associated gastrointestinal tract malignancies\(^52\)–\(^54\). Genistein also reduced the growth and proliferation of gastric cancer cells by cell cycle arrest and the Akt signaling pathway, which increased apoptosis and inhibited angiogenesis\(^55\)–\(^57\).

Interestingly, this protective effect was only found for soy product consumption but not for the mixed exposure. Of all of the included studies, seven studies reported the association between soy product consumption...
and the incidence of gastric cancer. Wada et al. and Hara et al. reported this association in females and males, respectively. Thus, we considered them to be two independent studies. Those seven studies that had a clear statement on the measurement of the intake of the mixed types of soybean products are shown in Table 1. However, there were three studies that reported the relationship between miso soup consumption and the incidence of gastric cancer. When we combined those three studies with the previous seven studies that included a mixed exposure, the above-mentioned protective effect was not observed. Miso soup is a traditional Japanese food with high salt that is made from fermented soybeans. The fermented soy foods contain N-nitroso compounds. High concentrations of sodium in the diet were reported to enhance the carcinogenicity of N-nitroso compounds and H. pylori infection, as well as weaken the protective effect of the mucous barrier.

In our study, the beneficial effect of soy consumption was found among the female population but not among the male population. Chandanos et al. reported that women with a longer fertility life and those who are on hormone replacement therapy seem to have a decreased risk of gastric cancer, and men who have been treated with estrogen for prostate cancer also have a decreased risk. The mechanism for this decrease in risk remains unknown. Isoflavones have a similar structure to 17β-estradiol and act as estrogen agonists or antagonists in environments of different estrogen levels, which may contribute to the different beneficial effects of soy consumption in females and males.

Moderate heterogeneity was found from some of our results. First, while every study adjusted for age and gender in the calculation of risk estimates, not every included study has been adjusted for total energy intake and body mass index, which are confounding factors. Second, the effects that soy intake has on GI cancer risk might differ among different preparations or fermentations of soy foods. Three included studies adjusted and analyzed fermented and non-fermented soy food. The high intake of non-fermented soy food was more likely to be inversely associated with gastric cancer risk. A higher salt intake increased the risk of GI cancer, and miso soup, one of the soy subtypes, was considered a high salt food. Third, the data gathering methods that were used might also contribute to the heterogeneity. Four studies relied on a personal interview, while the remaining studies came from the self-reported Food Frequency Questionnaires (FFQ). The participants may have different understandings of the questionnaire by different methods. Fourth, thirteen studies used a validated FFQ mixed with nine non-validated FFQs. The validated FFQ listed various types of soy foods, leading to precise estimates of soy or isoflavone intake. Fifth, we have pooled cohort studies and a nested case-control study with different estimates of OR, RR and HR. HR and OR were considered to be approximations of RR because CRC is a rare outcome in humans. We used a random effects method to determine when the heterogeneity was larger than 40% to enhance the credibility of the results.

Our meta-analysis has several strengths. First, our study was based on only prospective studies, which enabled us to minimize the food exposure recall bias and selection bias. To our knowledge, this is the first time that the association between both GI cancer incidence and mortality with soy intake from prospective studies has been summarized. Most previous meta-analyses collected both retrospective and prospective studies. Woo et al. reported that a case-control design created a significant association between the flavonoid subclasses and cancer risk, while cohort studies did not observe this association. Second, all included studies strictly followed our inclusion criteria, which made our results more stable. Third, our sample size is an important strength, as we included a total of 12,901 cancer cases from a total of 965,466 participants. Combining a large number of participants renders us sufficient power to detect potential, modest associations. Fourth, according to our sensitivity analysis, the inverse association did not vary with the exclusion of any single study.
Similar to all other meta-analyses, our study has some limitations. First, moderate heterogeneity was observed from some of our results. We have discussed the reasons above; however, the sensitivity analysis showed that our inverse association was stable and reliable. Second, the included studies were reported from different countries and populations and the measurement of soy intake and soy type varied among them.

In summary, no association was found between soy consumption and GI cancer incidence or mortality. A higher intake of soy product is associated with the decreased risk of overall GI cancer and gastric cancer, but not colorectal cancer. This protective effect was observed in females but not in males.

Methods

Search strategy. We systematically searched three databases, PubMed, ISI web of science and EMBASE, for studies that were published in any language (up until December 7, 2016). We combined the key words of the three following items: terms for outcome (colorectal cancer, gastric cancer, or gastrointestinal cancer), terms for exposure (soy product or isoflavone), and terms for epidemiology (cohort, prospective, or observational study).

According to the key words of the medical subject headings (MeSH), we searched the following MeSH: colorectal cancer, colorectal carcinoma, colorectal neoplasm(s), colorectal tumor(s), colon cancer, colon carcinoma, colon neoplasm(s), colon tumor(s), colonic cancer, colonic carcinoma, colonic neoplasm(s), colonic tumor(s), rectal cancer, rectal carcinoma, rectal neoplasm(s), rectal tumor(s), stomach cancer, stomach carcinoma, stomach neoplasm(s), stomach tumor(s), gastric cancer, gastric carcinoma, gastric neoplasm(s), gastric tumor(s), gastrointestinal cancer, gastrointestinal carcinoma, gastrointestinal neoplasm(s), gastrointestinal tumor(s), soy, tofu, miso, soybean, soymilk, natto, isoflavone, coumestrol, genistein, pterocarpans, daidzein, cohort, prospective, and observational study. This search was restricted to studies that used human participants.

In addition, we reviewed the reference lists of all of the eligible studies to identify more potential studies.

Study selection. The following inclusion criteria were applied in the screening of articles: (1) original reported data that evaluated the association between soy consumption and GI cancer incidence or mortality, (2) studies with a prospective study design, (3) studies that used risk point estimates, e.g., odds ratio (OR), relative risk (RR) or hazard ratio (HR) estimates with 95% confidence intervals (CIs), and (4) studies with population-based control samples. We did not include the studies that reported the associations between the serum concentrations of isoflavones and GI risk. When there were multiple published reports from the same study population, the most recent or the most informative report was selected for analysis.

Data extraction. The extracted data that were used included the first author’s name, year of publication, participants’ ages, study name, location, sample size, cancer type, study period, method used for the food intake measurements, validity of FFQ, method used in the cancer and/or death ascertainment, exposure items, soy consumption type, the risk estimates or data used to calculate the risk estimates, 95% CIs and adjustments for potential confounding effects. When more than one adjusted ratio was reported, the ratio with the most adjustment variables was chosen.

Credibility of meta-analysis results. We performed this meta-analysis under the guidance of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE). All enrolled studies were in strict compliance with well-designed inclusion criteria and exclusion criteria. To protect from bias, there was no change of results when any of the studies were excluded by the sensitivity analysis. Two observers independently evaluated the quality and eligibility of the included studies.

Statistical analysis. We extracted the association between soy consumption and GI cancer incidence or mortality by the ORs, RRs or HRs that were reported in the included studies. Soy type was defined as being one of three subgroups: soy product, isoflavone or miso soup. When more than one adjusted ratio was reported, the ratio with the most adjustment variables was chosen. ORs, RRs or HRs and 95% CIs were estimated based on the most adjusted variables for the highest versus the lowest soy consumption. In situations where the incidence was low, the odds ratio approximates the relative risk and hazard ratio. Therefore, for studies of GI cancer (a rare event), it is acceptable to compare the OR, RR and HR estimates. The outcomes are presented as a forest plot with the 95% CIs.

We used $I^2$ and Cochrane Q statistics, which are quantitative measures of inconsistency among studies, to test for possible heterogeneity across the studies. When $I^2$ was from 0% to 40% and had a $P > 0.10$, the heterogeneity might not be important. If the meta-analysis has no heterogeneity, a fixed-effects model with the Mantel–Haenszel method would be used to combine the individual studies. Otherwise, the random-effects method was used for pooling.

To estimate multiple modification effects, cancer site-specific, gender-specific and soy type-specific analyses were performed. Additionally, we did a single study sensitivity analysis for each of the statistically significant results. Sensitivity analyses were conducted by excluding each study, in turn, to evaluate the stability of the results.

The Egger’s regression test and Begg–Mazumdar test were used to assess for publication bias. $P < 0.05$ was considered to be a statistically significant publication bias.

All reported P-values were two-sided. All statistical analyses were performed using STATA (version 11.0; Stata-Corp, College Station, TX).
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Acknowledgements
The authors thank Dr. Zuoxu Fan of the Department of Neurology, First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China for his contributions and guidance. This study was supported by the Training Program of the Major Research Plan of the National Natural Science Foundation of China, No. 91229104, Key Projects in the National Science & Technology Pillar Program during the Twelfth Five-year Plan Period, No. 2014BA109B07, National High Technology Research and Development Program of China (863 Program), No. 2012AA02A506, National High Technology Research and Development Program of China (863 Program), No. 2012AA02A204, Zhejiang Provincial Natural Science Foundation of China, NO. LQ14H160010, and National Natural Science Foundation of China, NO. 81502598.

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Demin Lu, Chi Pan, Chenyang Ye and Suzhan Zhang wrote the main manuscript text. Huijie Duan and Fei Xu prepared the tables. Li Yin, Kaixin Hu and Wei Tian made the figures. All of the authors reviewed the manuscript.
