Soy and isoflavone intake associated with reduced risk of ovarian cancer in southern Chinese women

Andy H. Lee[1], Dada Su[1], Maria Pasalich[1], Li Tang[1], Colin W. Binns[1], Liqian Qiu[2]

[1] School of Public Health, Curtin University, Perth, WA, Australia

[3] Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China

Corresponding author:

Professor Andy H. Lee

School of Public Health

Curtin University

GPO Box U 1987

Perth, WA, 6845, Australia

Phone: +61-8-92664180

Fax: +61-8-92662958

Email: Andy.Lee@curtin.edu.au

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ABBREVIATIONS

CI; confidence interval

MET; metabolic equivalent task

OR; odds ratio

ABSTRACT

Isoflavones, mainly found in soy, have been shown to inhibit ovarian cancer cell proliferation. We hypothesized that soy consumption and isoflavone intake are related to the risk of ovarian cancer. A case-control study was conducted in southern China to ascertain this hypothesis. Five hundred incident patients with histologically confirmed cancer of the ovary and 500 controls (mean age 59 years) were recruited from four public hospitals in Guangzhou. Information on habitual consumption of soy foods, including soybean, soy milk, fresh tofu, dried tofu and soybean sprout, was obtained face-to-face from participants through a validated and reliable semi-quantitative food frequency questionnaire. Isoflavone intakes were then estimated using the USDA nutrient database. The ovarian cancer patients reported lower consumption levels of individual and total soy foods (75.3 ± 53.6 g/day) than the controls (110.7 ± 88.8 g/day). Logistic regression analyses showed that regular intake of soy foods could reduce the ovarian cancer risk, the adjusted odds ratio being 0.29 (95% confidence interval 0.20 to 0.42) for women who consumed at least 120 g/day relative to those less than 61 g/day. Similarly, isoflavone intakes were inversely associated with the ovarian cancer risk, with significant dose-response relationships ($P < 0.001$). We concluded that consumption of soy foods is associated with a reduced risk of ovarian cancer in southern Chinese women.

Keywords: case-control study, women, daidzein, genistein, glycitein, isoflavone, soy foods

1. INTRODUCTION

Ovarian cancer has the eighth highest incidence of all cancers in women [1], and is the second most common gynecological malignancy [2]. The 5-year prevalence rate for ovarian cancer has exceeded half a million cases worldwide [1]. Considerable geographic variations exist in the incidence of ovarian cancer, with higher rates reported in developed countries. The age-standardized rates in Europe and the United States are 10.1 and 8.8 per 100,000 women, respectively, but only 3.8 per 100,000 women in China [1]. The difference in incidence rates between countries has generated interest in the role of dietary and lifestyle factors in ovarian cancer etiology, apart from genetic and familial risk factors, which may lead to health promotion strategies for the primary prevention of the disease.

Soy food products are widely consumed in Asian countries, and soy is a primary source of isoflavones. Previous research has suggested soy consumption may prevent the development of ovarian cancer. A meta-analysis demonstrated the protective effect of soy, with odds ratio (OR) 0.52 (95% confidence interval (CI) 0.42 to 0.66) for the highest versus the lowest level of intake [3]. Similarly, an Italian multicenter case-control study reported a 41% risk reduction for women with the highest intake of specific seed oils, such as soya [4]. For isoflavones, a large prospective cohort study in the USA observed a relative risk of 0.56 for daily intake of total isoflavones above 3 mg, when compared to below 1 mg per day [5]. Another case-control study undertaken in Hangzhou, China, found significant inverse associations between the ovarian cancer risk and intake of soy foods and specific isoflavones [6]. However, two population-based cohort studies conducted in the USA and Sweden found little association between the intake of phytoestrogens or phytoestrogen/flavonoid-rich foods and the ovarian cancer incidence [7, 8], which could be attributed to the low consumption of soy products among adults in these countries. Given that soy food products are widely consumed in China and the biologically plausible cancer protective mechanisms of isoflavones, we hypothesized that soy and isoflavone intake is associated with a reduced risk of ovarian cancer in southern Chinese women.

Several types of soy foods are popular in southern China, including soybean, soy milk (produced by soaking and grinding dried soybeans) and tofu (fermented product of soy milk). In view of the conflicting epidemiological evidence, the present study aimed to assess the association between habitual soy food consumption, isoflavone intake and the risk of ovarian cancer among southern Chinese women.

2. METHODS AND MATERIALS

2.1 Study design and participants

A hospital-based 1:1 case-control study was conducted in Guangzhou, the capital city of Guangdong Province of southern China, between August 2006 and July 2008. Subjects were recruited from four public hospitals, namely, The Overseas Hospital (affiliated with Jinan University), Zhujiang Hospital, General Hospital of Guangzhou Military Command, and Second Affiliated Hospital of Zhongshan University. Cases were incident patients who had been histopathologically diagnosed with cancer of the ovary within the past 12 months and resided in the metropolitan Guangzhou area for at least the past ten years.

Potential cases were identified by searching the daily census of the hospitals. To ensure complete ascertainment of cases, all hospital medical records and laboratory pathology reports were reviewed during the recruitment period. Pathological diagnoses were based on the International Histological Classification of Ovarian Tumors [9]. Patients were excluded when ovarian cancer was histopathologically confirmed to be neither the primary nor final diagnosis, over 75 years of age, or if they confessed to have memory problems affecting their recall of past events. Of the total 504 cases consecutively recruited from the four hospitals, 500 patients with cancer of the ovary consented to participate and were capable of being interviewed.

During the same period, 512 eligible controls were recruited from inpatient wards of the Departments of ophthalmology, orthopedic, respiratory disease, gastroenterology and physiotherapy. These women were group matched to cases within 5 years of age. Exclusion criteria for controls were (i) previous diagnosis of ovarian cancer or other malignant diseases; (ii) a history of bilateral oophorectomy; (iii) having memory problems; (iv) on long-term modification of diet for medical reasons; in addition to non-Guangzhou resident and age over 75 years. Subjects to be approached for inclusion as controls were initially screened using the hospital daily census sheets. A selection of ward and patient ID was made using random numbers each day whenever more control subjects appeared to be available than could be interviewed. All eligible inpatients had their diagnosis subsequently confirmed by histopathological reports to avoid misclassification of the case-control status. This systematic selection process was adopted throughout the recruitment period. Twelve women who declined the interview or did not satisfy the eligibility conditions were later excluded, resulting in a final sample of 500 controls available for analysis. No statistically significant differences were found between the two groups in terms of age and main demographic variables.

2.2 Interview

An appointment for a face-to-face interview was then arranged with each participant in conjunction with the nursing staff to avoid interference with treatment at the ward and before being discharged from hospital. Whenever possible, subjects were interviewed in the presence of their next-of-kin to help the recall of dietary habits. All participants gave formal consent before the interview. They were also assured of confidentiality and their right to withdraw without prejudice. Each interview, conducted in either Mandarin or the Cantonese dialect, took about 45 minutes to complete. All participants were blinded to the study hypothesis. The project protocol was approved by the participating hospitals, the doctors-in-charge of the relevant wards, and the Human Research Ethics Committee of Curtin University (approval number HR 78/2006).

2.3 Questionnaire and exposure measurements

A structured questionnaire was administered to obtain demographic and lifestyle characteristics including age, weight (kg), height (m), education level, smoking status and alcohol consumption, as well as reproductive history, hormonal status and heredity. Self-reported data were cross-checked with medical records whenever available.

Participants were also requested to estimate their average time engaged in physical activities using validated questions [10]. Intensity was classified by the amount of energy or effort a person expends in performing the activity. Physical activity at each intensity level was quantified in terms of metabolic equivalent tasks (MET)-hours per week, with intensity codes 7.5, 6.0 and 4.5 MET assigned to strenuous sports, vigorous work and moderate activity, respectively. Total physical activity was then calculated by summing the product of MET score and activity duration over the three intensity levels.

Information on habitual food and beverage consumption was obtained using a 125-item semi-quantitative food frequency questionnaire developed and tested for the southern Chinese population [11, 12, 13]. This validated instrument covered commonly consumed foods (including soy products) in southern China. Frequency and amount of intake were recorded in detail. The reference recall period for dietary variables was set at five years before diagnosis for cases and five years before interview for controls. The energy content of each food or beverage item was obtained from the Chinese food composition tables [13]. We then estimated participants' total energy intake (kcal) by summing the energy intake across individual items consumed.

2.4 Statistical analyses

Descriptive statistics were first used to compare the sample characteristics and soy consumption variables between case and control groups. Unconditional logistic regression analyses were then performed to investigate the effects of total and individual soy foods on the ovarian cancer risk. Total soy intake (g/day) was defined as the sum of daily consumption of soybean, soy milk, soybean sprout, fresh tofu and dried tofu. Soy sauce was excluded, because it was typically added during cooking and thus difficult to quantify the exact amount consumed. Daily intakes (mg) of daidzein, genistein, glycitein, and total isoflavones were estimated based on the soy foods intake using the USDA nutrient database [14], as they were not available from the Chinese food composition tables. For each soy and isoflavone variable, the corresponding tertiles among controls were used to derive the cut points, resulting in three increasing levels of exposure, with the lowest level of intake being the reference category.

In addition to reporting crude and adjusted OR and associated 95% CI according to tertiles, tests for linear trend were conducted to assess the dose-response relationship between habitual soy consumption, isoflavone intake and the ovarian cancer risk. Confounding variables included in the logistic regression models were age at interview (years), parity, oral contraceptive use (never, ever), body mass index (5 years ago), menopausal status (pre, post), education level (none or primary, secondary, vocational or tertiary), tobacco smoking (never, ever), alcohol drinking (no, yes), hormone replacement therapy (no, yes), physical activity (5 years ago, MET-hours/week), total energy intake (quintiles, kcal/day), and family history of ovarian or breast cancer (no, yes). These variables were either established or plausible risk factors from the literature. All statistical analyses were undertaken using the SPSS package version 20.

3. RESULTS

Table 1 presents characteristics of the sample by case-control status. The participants were 59 years of age on average and predominantly post-menopausal. Most of them had attained secondary school education or above, were non-smokers and seldom drank alcoholic beverages on a regular basis. Very few women had a family history of ovarian or breast cancer. Women with ovarian cancer tended to have less oral contraceptive use and lower parities but higher mean body mass index than their counterparts without the disease. The two groups were also different with respect to physical activity in daily life.

Table 2 compares the habitual soy and isoflavone intake between case and control groups. The ovarian cancer patients reported lower consumption levels of individual and total soy foods (75.3 $\pm$53.6 g/day) than the control subjects (110.7 $\pm$88.8 g/day). According to univariate *t* tests, the levels of isoflavone intake were significantly lower among cases when compared to controls.

Table 3 summarizes the results of logistic regression analyses. Substantial reductions in ovarian cancer risk were evident for high consumptions of all soy products. Overall, the adjusted OR was 0.29 (95% CI 0.20 to 0.42) for women who consumed at least 120 g of soy foods per day relative to those less than 61 g per day. Higher intakes of soy milk, tofu, soybean and soybean sprout were associated with reduced risks of ovarian cancer when comparing the highest versus lowest tertiles. The corresponding linear trends were significant except for soybean. Similarly, isoflavone intakes were inversely associated with the ovarian cancer risk, with significant dose-response relationships (*P* for trend < 0.001) observed for daidzein, genistein and glycitein. The ORs were approximately 0.40 for the highest versus the lowest tertiles of daidzein, genistein and glycitein intakes. Further sensitivity analyses with categorical body mass index (5 years ago, < 18.5, 18.5-22.9, ≥ 23 kg/m^2) [15] and physical activity (5 years ago, tertiles, MET-hours/week) produced similar results.

4. DISCUSSION

This case-control study of southern Chinese women suggested that habitual consumption of soy foods could lead to reductions in ovarian cancer risk after controlling for plausible confounding variables. The finding confirmed our research hypothesis. A previous study undertaken in Hangzhou, China, reported similar inverse associations between soy products, isoflavones and the ovarian cancer risk [6]. The present study considered more soy food items (soy milk and soybean sprout) and was conducted in a different geographic area in China, thus adding further epidemiological evidence on the potential protective role of soy foods against ovarian cancer. Our findings are consistent with a meta-analysis of four epidemiologic studies, which found a 48% decreased risk of ovarian cancer for the highest soy intake compared to the lowest intake [3]. Two of the included studies were conducted in China and Japan, countries with high consumption of soy products. A recent Italian case-control study also observed a reduced risk, with adjusted OR 0.51 (95% CI 0.37 to 0.69) comparing the highest versus the lowest quintile of isoflavone intake [16]. On the contrary, two prospective cohort studies conducted in USA and Sweden found no evidence for a protective effect [7, 8]. It should be remarked that tofu was the only soy item assessed among the selected flavonoid-rich foods [7], while the consumption of soy foods was generally low in the Swedish population [8]. Differences in study design, food sources and consumption level between populations may partly explain the conflicting epidemiological findings.

The protective effect of soy and isoflavone is biologically plausible and supported by experimental evidence. Ovarian cancer is an estrogen-dependent cancer. Phytoestrogens found in plant foods, such as isoflavones, have been shown to induce apoptosis and inhibit growth and proliferation of ovarian cancer cells [17-19]. These compounds are structurally related to endogenous estrogen [20]. They may stimulate the production of sex hormone-binding globulin in the liver, which in turn causes levels of bioavailable estrogens to decrease [21]. Another plausible mechanism is through the inhibition of ovarian aromatase activity, an enzyme which converts androgens to estrogen, as demonstrated by an in vitro study [22].

In this study, habitual food consumption was measured using a validated and reliable questionnaire specifically developed for the southern Chinese population, with information on frequency and quantity of intake recorded in detail. To determine and ascertain the effect of soy and isoflavone, information on other exposures and confounding factors such as tobacco smoking, alcohol drinking and physical activity was also collected. The sample size of 1000 participants ensured sufficient power for the analysis. Another strength of the study was the inclusion of only incident patients diagnosed with ovarian cancer within the past 12 months. All controls had been carefully screened and subsequently confirmed with pathology to avoid misclassification of the case-control status. It is possible that some ovarian cancer patients may modify their dietary habits since the onset of the disease. To avoid reverse causation, the reference period for habitual soy consumption was set at five years before diagnosis for cases and five years before interview for controls. Moreover, no participant reported any change in eating habits for medical reasons within the past five years.

A major limitation concerns the inherent retrospective case-control design so that any cause-effect relationship could not be established. Although the recall of habitual soy consumption should not be affected by the case-control status, dietary assessment was based on self-report and the recall period was set at five years, so that responses from participants would inevitably incur some recall error which might impact on the reliable estimation of effects. Therefore, face-to-face interviews were conducted in the presence of their next-of-kin to help memory recall and to improve the accuracy of their answers. Selection bias was unavoidable because all participants were voluntary and the hospital-based controls were not randomly selected from the community. Nevertheless, the four participating hospitals serve the entire catchment region so that our subjects were still representative of the target population. Recruitment bias was also minimized by sampling from different hospitals. Information bias and recall bias were unlikely because all participants were blind to the study hypothesis, while the potential protective effects of soy products against ovarian cancer have not been established in southern China at the time of interview. Finally, residual confounding might still exist even though established risk factors have been controlled for in the multivariable logistic regression analyses. There is no evidence from the literature supporting soy consumption as a marker of healthy lifestyle among southern Chinese women.

In conclusion, an inverse association was found between higher soy consumption and the risk of ovarian cancer in southern China, with significant dose-response relationships observed for total and specific isoflavone intake. Further studies are required before generalizing the findings to other populations, and to confirm whether long term consumption of soy products can offer protection and enhance the survival of this deadly disease.

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Table 1.

Characteristics of participants by case-control status for southern Chinese women

Variable	Cases		Controls		
	n	(%)	n	(%)	P [a]
Body mass index (5 years ago, kg/m^2)					< 0.05
< 18.5	36	(7.2)	46	(9.2)	
18.5-22.9	348	(69.6)	373	(74.6)	
≥ 23.0	116	(23.2)	81	(16.2)	
Physical activity (5 years ago, MET-hours/week)					< 0.01
≤ 11.5	287	(57.4)	226	(45.2)	
11.6-22.5	133	(26.6)	133	(26.6)	
> 22.5	80	(16.0)	141	(28.2)	
Education level					0.90
None/primary	204	(40.8)	197	(39.4)	
Secondary	171	(34.2)	175	(35.0)	
Vocational/tertiary	125	(25.0)	128	(25.6)	
Tobacco smoking					0.49
Never	481	(96.2)	485	(97.0)	
Ever	19	(3.8)	15	(3.0)	
Alcohol drinking					0.16
No	352	(70.4)	372	(74.4)	
Yes	148	(29.6)	128	(25.6)	
Parity					< 0.01
0	8	(1.6)	14	(2.8)	
1	172	(34.4)	143	(28.6)	
2	219	(43.8)	176	(35.2)	
≥ 3	101	(20.2)	167	(33.4)	
Oral contraceptive use					< 0.01
Never	417	(83.4)	380	(76.0)	
Ever	83	(16.6)	120	(24.0)	
Hormone replacement therapy					1.00
No	493	(98.6)	493	(98.6)	
Yes	7	(1.4)	7	(1.4)	
Menopausal status					0.24
Pre	28	(5.6)	20	(4.0)	
Post	472	(94.4)	480	(96.0)	
Family history of ovarian or breast cancer					0.39
No	480	(96.0)	485	(97.0)	
Yes	20	(4.0)	15	(3.0)	
Age at interview (years) [b]	59.07	± 5.68	59.71	± 6.46	0.10
Body mass index (5 years ago, kg/m^2) [b]	21.70	± 2.54	21.12	± 2.28	< 0.01
Physical activity (5 years ago, MET-hours/week) [b]	16.21	± 14.1	18.84	± 13.0	< 0.01

[a] Chi-square or t-test for difference between cases and controls

[b] Values are means ± SD

Table 2.

Comparison of soy consumption and isoflavone intake between case and control groups among southern Chinese women

Daily intake [a]	**Cases**	**Controls**	*P* [b]
Total soy foods (g)	75.3 ± 53.6	110.7 ± 88.8	< 0.001
Soy milk (ml)	31.1 ± 41.2	48.9 ± 56.6	< 0.001
Fresh tofu (g)	10.0 ± 15.0	14.7 ± 21.0	< 0.001
Dried tofu (g)	5.2 ± 10.1	7.0 ± 18.6	0.053
Soybean (g)	11.3 ± 14.3	14.5 ± 18.5	0.002
Soybean sprout (g)	17.8 ± 16.1	25.6 ± 31.9	< 0.001
Isoflavones (mg)	30.3 ± 22.2	41.7 ± 36.2	< 0.001
Daidzein (mg)	12.4 ± 9.3	17.0 ± 14.7	< 0.001
Genistein (mg)	15.5 ± 11.2	21.4 ± 18.9	< 0.001
Glycitein (mg)	2.4 ± 1.9	3.3 ± 2.9	< 0.001

[a] Values are means ± SD

[b] t-test for mean difference between cases and controls

Table 3.

Crude and adjusted odds ratios and 95% confidence intervals (CI) of ovarian cancer risk according to tertiles of soy consumption and isoflavone intake among southern Chinese women

Daily intake	**Cases** n (%)	**Controls** n (%)	**Crude OR** (95% CI)	**Adjusted OR** [a] (95% CI)	*P* for trend [a]
Total soy foods (g)					< 0.001
≤ 61.4	267 (53.4%)	167 (33.4%)	1.00	1.00	
61.5-119.0	158 (31.6%)	167 (33.4%)	0.59 (0.44, 0.79)	0.63 (0.46, 0.86)	
> 119.0	75 (15.0%)	166 (33.2%)	0.28 (0.20, 0.40)	0.29 (0.20, 0.42)	
Soy milk (ml)					< 0.001
≤ 12.9	294 (58.8%)	218 (43.6%)	1.00	1.00	
13.0-38.6	117 (23.4%)	129 (25.8%)	0.67 (0.50, 0.91)	0.66 (0.47, 0.91)	
> 38.6	89 (17.8%)	153 (30.6%)	0.43 (0.32, 0.59)	0.43 (0.31, 0.60)	
Tofu [b] **(g)**					< 0.001
≤ 8.6	228 (45.6%)	193 (38.6%)	1.00	1.00	
8.7-20.0	175 (35.0%)	158 (31.6%)	0.94 (0.70, 1.25)	1.00 (0.73, 1.36)	
> 20.0	97 (19.4%)	149 (29.8%)	0.55 (0.40, 0.76)	0.57 (0.40, 0.80)	
Soybean (g)					0.067
≤ 5.4	325 (65.0%)	263 (52.6%)	1.00	1.00	
5.5-10.7	70 (14.0%)	90 (18.0%)	0.63 (0.44, 0.90)	0.60 (0.41, 0.87)	
> 10.7	105 (21.0%)	147 (29.4%)	0.58 (0.43, 0.78)	0.62 (0.45, 0.85)	
Soybean sprout (g)					< 0.001
≤ 8.9	293 (58.6%)	247 (49.4%)	1.00	1.00	
9.0-26.8	166 (33.2%)	169 (33.8%)	0.83 (0.63, 1.09)	0.80 (0.59, 1.06)	
> 26.8	41 (8.2%)	84 (16.8%)	0.41 (0.27, 0.62)	0.43 (0.27, 0.67)	
Isoflavones (mg)					< 0.001
≤ 26.7	258 (51.6%)	166 (33.2%)	1.00	1.00	
26.8-41.0	146 (29.2%)	168 (33.6%)	0.56 (0.42, 0.75)	0.53 (0.39, 0.74)	
> 41.0	96 (19.2%)	166 (33.2%)	0.37 (0.27, 0.51)	0.45 (0.29, 0.59)	
Daidzein (mg)					< 0.001
≤ 10.2	263 (52.6%)	167 (33.4%)	1.00	1.00	
10.3-16.9	141 (28.2%)	168 (33.6%)	0.53 (0.40, 0.72)	0.50 (0.36, 0.69)	

> 16.9	96 (19.2%)	165 (33.0%)	0.37 (0.27, 0.51)	0.41 (0.29, 0.59)	
Genistein (mg)					< 0.001
≤ 12.3	256 (51.2%)	167 (33.4%)	1.00	1.00	
12.4-21.1	147 (29.4%)	167 (33.4%)	0.57 (0.43, 0.77)	0.56 (0.40, 0.77)	
> 21.1	97 (19.4%)	166 (33.2%)	0.38 (0.28, 0.52)	0.42 (0.30, 0.60)	
Glycitein (mg)					< 0.001
≤ 1.9	265 (53.0%)	166 (33.2%)	1.00	1.00	
2.0-3.3	143 (28.6%)	168 (33.6%)	0.53 (0.40, 0.72)	0.52 (0.38, 0.71)	
> 3.3	92 (18.4%)	166 (33.2%)	0.35 (0.25, 0.48)	0.38 (0.27, 0.55)	

[a] From separate unconditional logistic regression models adjusting for age (years, continuous), body mass index (5 years ago, kg/m^2, continuous), physical activity (5 years ago, MET-hours/week, continuous), total energy intake (kcal/day, quintiles), parity (continuous), oral contraceptive use (never, ever), hormone replacement therapy (no, yes), menopausal status (pre, post), education (none/primary, secondary, vocational/tertiary), smoking status (never, ever), alcohol drinking (no, yes), and family history of ovarian or breast cancer (no, yes).

[b] Sum of fresh tofu and dried tofu due to small quantities consumed for the latter

Supplemental Table 1.

Crude and adjusted odds ratios and 95% confidence intervals (CI) of ovarian cancer risk according to tertiles of soy consumption and isoflavone intake among southern Chinese women

Daily intake	Cases n (%)	Controls n (%)	Crude OR (95% CI)	Adjusted OR [a] (95% CI)	*P* for trend [a]
Total soy foods (g)					< 0.001
≤ 61.4	267 (53.4%)	167 (33.4%)	1.00	1.00	
61.5-119.0	158 (31.6%)	167 (33.4%)	0.59 (0.44, 0.79)	0.61 (0.45, 0.84)	
> 119.0	75 (15.0%)	166 (33.2%)	0.28 (0.20, 0.40)	0.29 (0.20, 0.42)	
Soy milk (ml)					< 0.001
≤ 12.9	294 (58.8%)	218 (43.6%)	1.00	1.00	
13.0-38.6	117 (23.4%)	129 (25.8%)	0.67 (0.50, 0.91)	0.61 (0.44, 0.85)	
> 38.6	89 (17.8%)	153 (30.6%)	0.43 (0.32, 0.59)	0.43 (0.30, 0.60)	
Tofu [b] (g)					0.001
≤ 8.6	228 (45.6%)	193 (38.6%)	1.00	1.00	
8.7-20.0	175 (35.0%)	158 (31.6%)	0.94 (0.70, 1.25)	1.01 (0.74, 1.38)	
> 20.0	97 (19.4%)	149 (29.8%)	0.55 (0.40, 0.76)	0.60 (0.42, 0.85)	
Soybean (g)					0.102
≤ 5.4	325 (65.0%)	263 (52.6%)	1.00	1.00	
5.5-10.7	70 (14.0%)	90 (18.0%)	0.63 (0.44, 0.90)	0.58 (0.40, 0.84)	
> 10.7	105 (21.0%)	147 (29.4%)	0.58 (0.43, 0.78)	0.62 (0.45, 0.86)	
Soybean sprout (g)					0.001
≤ 8.9	293 (58.6%)	247 (49.4%)	1.00	1.00	
9.0-26.8	166 (33.2%)	169 (33.8%)	0.83 (0.63, 1.09)	0.80 (0.59, 1.07)	
> 26.8	41 (8.2%)	84 (16.8%)	0.41 (0.27, 0.62)	0.45 (0.29, 0.71)	
Isoflavones (mg)					< 0.001
≤ 26.7	258 (51.6%)	166 (33.2%)	1.00	1.00	
26.8-41.0	146 (29.2%)	168 (33.6%)	0.56 (0.42, 0.75)	0.53 (0.38, 0.73)	
> 41.0	96 (19.2%)	166 (33.2%)	0.37 (0.27, 0.51)	0.43 (0.30, 0.62)	
Daidzein (mg)					< 0.001
≤ 10.2	263 (52.6%)	167 (33.4%)	1.00	1.00	
10.3-16.9	141 (28.2%)	168 (33.6%)	0.53 (0.40, 0.72)	0.50 (0.36, 0.69)	
> 16.9	96 (19.2%)	165 (33.0%)	0.37 (0.27, 0.51)	0.43 (0.30, 0.61)	

Genistein (mg)					< 0.001
≤ 12.3	256 (51.2%)	167 (33.4%)	1.00	1.00	
12.4-21.1	147 (29.4%)	167 (33.4%)	0.57 (0.43, 0.77)	0.56 (0.40, 0.77)	
> 21.1	97 (19.4%)	166 (33.2%)	0.38 (0.28, 0.52)	0.44 (0.31, 0.62)	
Glycitein (mg)					< 0.001
≤ 1.9	265 (53.0%)	166 (33.2%)	1.00	1.00	
2.0-3.3	143 (28.6%)	168 (33.6%)	0.53 (0.40, 0.72)	0.51 (0.37, 0.70)	
> 3.3	92 (18.4%)	166 (33.2%)	0.35 (0.25, 0.48)	0.40 (0.28, 0.56)	

[a] From separate unconditional logistic regression models adjusting for age (years, continuous), body mass index (5 years ago, < 18.5, 18.5-22.9, ≥ 23 kg/m^2), physical activity (5 years ago, tertiles, MET-hours/week), total energy intake (kcal/day, quintiles), parity (continuous), oral contraceptive use (never, ever), hormone replacement therapy (no, yes), menopausal status (pre, post), education (none/primary, secondary, vocational/tertiary), smoking status (never, ever), alcohol drinking (no, yes), and family history of ovarian or breast cancer (no, yes).

[b] Sum of fresh tofu and dried tofu due to small quantities consumed for the latter

Supplemental Table 2.

Crude and adjusted odds ratios and 95% confidence intervals (CI) of ovarian cancer risk according to tertiles of soy consumption and isoflavone intake among southern Chinese women

Daily intake	**Cases** n (%)	**Controls** n (%)	**Crude OR** (95% CI)	**Adjusted OR** [a] (95% CI)	*P* for trend [a]
Total soy foods (g)					< 0.001
≤ 61.4	267 (53.4%)	167 (33.4%)	1.00	1.00	
61.5-119.0	158 (31.6%)	167 (33.4%)	0.79 (0.65, 0.96)	0.84 (0.68, 1.02)	
> 119.0	75 (15.0%)	166 (33.2%)	0.51 (0.39, 0.66)	0.55 (0.42, 0.71)	
Soy milk (ml)					< 0.001
≤ 12.9	294 (58.8%)	218 (43.6%)	1.00	1.00	
13.0-38.6	117 (23.4%)	129 (25.8%)	0.84 (0.68, 1.04)	0.85 (0.68, 1.05)	
> 38.6	89 (17.8%)	153 (30.6%)	0.63 (0.50, 0.81)	0.67 (0.52, 0.85)	
Tofu [b] **(g)**					0.009
≤ 8.6	228 (45.6%)	193 (38.6%)	1.00	1.00	
8.7-20.0	175 (35.0%)	158 (31.6%)	0.98 (0.80, 1.19)	1.01 (0.83, 1.23)	
> 20.0	97 (19.4%)	149 (29.8%)	0.73 (0.58, 0.93)	0.77 (0.60, 0.98)	
Soybean (g)					0.224
≤ 5.4	325 (65.0%)	263 (52.6%)	1.00	1.00	
5.5-10.7	70 (14.0%)	90 (18.0%)	0.79 (0.61, 1.02)	0.79 (0.61, 1.02)	
> 10.7	105 (21.0%)	147 (29.4%)	0.76 (0.61, 0.95)	0.81 (0.64, 1.01)	
Soybean sprout (g)					0.007
≤ 8.9	293 (58.6%)	247 (49.4%)	1.00	1.00	
9.0-26.8	166 (33.2%)	169 (33.8%)	0.91 (0.75, 1.10)	0.90 (0.75, 1.10)	
> 26.8	41 (8.2%)	84 (16.8%)	0.61 (0.44, 0.84)	0.65 (0.46, 0.91)	
Isoflavones (mg)					0.001
≤ 26.7	258 (51.6%)	166 (33.2%)	1.00	1.00	
26.8-41.0	146 (29.2%)	168 (33.6%)	0.77 (0.63, 0.94)	0.78 (0.63, 0.96)	
> 41.0	96 (19.2%)	166 (33.2%)	0.60 (0.48, 0.76)	0.66 (0.52, 0.84)	
Daidzein (mg)					0.001
≤ 10.2	263 (52.6%)	167 (33.4%)	1.00	1.00	
10.3-16.9	141 (28.2%)	168 (33.6%)	0.75 (0.61, 0.92)	0.75 (0.61, 0.93)	
> 16.9	96 (19.2%)	165 (33.0%)	0.60 (0.48, 0.76)	0.66 (0.52, 0.85)	

Genistein (mg)					0.001
≤ 12.3	256 (51.2%)	167 (33.4%)	1.00	1.00	
12.4-21.1	147 (29.4%)	167 (33.4%)	0.78 (0.64, 0.96)	0.79 (0.64, 0.98)	
> 21.1	97 (19.4%)	166 (33.2%)	0.61 (0.48, 0.77)	0.67 (0.52, 0.85)	
Glycitein (mg)					0.001
≤ 1.9	265 (53.0%)	166 (33.2%)	1.00	1.00	
2.0-3.3	143 (28.6%)	168 (33.6%)	0.75 (0.61, 0.92)	0.76 (0.62, 0.94)	
> 3.3	92 (18.4%)	166 (33.2%)	0.58 (0.46, 0.74)	0.64 (0.50, 0.82)	

[a] From separate conditional logistic regression models adjusting for body mass index (5 years ago, kg/m^2, continuous), physical activity (5 years ago, MET-hours/week, continuous), total energy intake (kcal/day, quintiles), parity (continuous), oral contraceptive use (never, ever), hormone replacement therapy (no, yes), menopausal status (pre, post), education (none/primary, secondary, vocational/tertiary), smoking status (never, ever), alcohol drinking (no, yes), and family history of ovarian or breast cancer (no, yes).

[b] Sum of fresh tofu and dried tofu due to small quantities consumed for the latter

Supplemental Table 3.

Crude and adjusted odds ratios and 95% confidence intervals (CI) of ovarian cancer risk according to tertiles of soy consumption and isoflavone intake among southern Chinese women

Daily intake	**Cases** n (%)	**Controls** n (%)	**Crude OR** (95% CI)	**Adjusted OR** [a] (95% CI)	*P* for trend [a]
Total soy foods (g)					< 0.001
≤ 61.4	267 (53.4%)	167 (33.4%)	1.00	1.00	
61.5-119.0	158 (31.6%)	167 (33.4%)	0.79 (0.65, 0.96)	0.82 (0.67, 1.00)	
> 119.0	75 (15.0%)	166 (33.2%)	0.51 (0.39, 0.66)	0.54 (0.41, 0.70)	
Soy milk (ml)					< 0.001
≤ 12.9	294 (58.8%)	218 (43.6%)	1.00	1.00	
13.0-38.6	117 (23.4%)	129 (25.8%)	0.84 (0.68, 1.04)	0.82 (0.66, 1.02)	
> 38.6	89 (17.8%)	153 (30.6%)	0.63 (0.50, 0.81)	0.65 (0.51, 0.83)	
Tofu [b] **(g)**					0.008
≤ 8.6	228 (45.6%)	193 (38.6%)	1.00	1.00	
8.7-20.0	175 (35.0%)	158 (31.6%)	0.98 (0.80, 1.19)	0.99 (0.81, 1.21)	
> 20.0	97 (19.4%)	149 (29.8%)	0.73 (0.58, 0.93)	0.76 (0.60, 0.97)	
Soybean (g)					0.206
≤ 5.4	325 (65.0%)	263 (52.6%)	1.00	1.00	
5.5-10.7	70 (14.0%)	90 (18.0%)	0.79 (0.61, 1.02)	0.77 (0.59, 1.00)	
> 10.7	105 (21.0%)	147 (29.4%)	0.76 (0.61, 0.95)	0.80 (0.64, 1.00)	
Soybean sprout (g)					0.005
≤ 8.9	293 (58.6%)	247 (49.4%)	1.00	1.00	
9.0-26.8	166 (33.2%)	169 (33.8%)	0.91 (0.75, 1.10)	0.92 (0.76, 1.11)	
> 26.8	41 (8.2%)	84 (16.8%)	0.61 (0.44, 0.84)	0.63 (0.45, 0.88)	
Isoflavones (mg)					< 0.001
≤ 26.7	258 (51.6%)	166 (33.2%)	1.00	1.00	
26.8-41.0	146 (29.2%)	168 (33.6%)	0.77 (0.63, 0.94)	0.78 (0.62, 0.95)	
> 41.0	96 (19.2%)	166 (33.2%)	0.60 (0.48, 0.76)	0.64 (0.50, 0.82)	
Daidzein (mg)					< 0.001
≤ 10.2	263 (52.6%)	167 (33.4%)	1.00	1.00	
10.3-16.9	141 (28.2%)	168 (33.6%)	0.75 (0.61, 0.92)	0.75 (0.61, 0.93)	
> 16.9	96 (19.2%)	165 (33.0%)	0.60 (0.48, 0.76)	0.64 (0.50, 0.82)	

Genistein (mg)					< 0.001
≤ 12.3	256 (51.2%)	167 (33.4%)	1.00	1.00	
12.4-21.1	147 (29.4%)	167 (33.4%)	0.78 (0.64, 0.96)	0.79 (0.64, 0.97)	
> 21.1	97 (19.4%)	166 (33.2%)	0.61 (0.48, 0.77)	0.65 (0.51, 0.83)	
Glycitein (mg)					0.001
≤ 1.9	265 (53.0%)	166 (33.2%)	1.00	1.00	
2.0-3.3	143 (28.6%)	168 (33.6%)	0.75 (0.61, 0.92)	0.76 (0.62, 0.93)	
> 3.3	92 (18.4%)	166 (33.2%)	0.58 (0.46, 0.74)	0.62 (0.49, 0.80)	

[a] From separate conditional logistic regression models adjusting for body mass index (5 years ago, < 18.5, 18.5-22.9, ≥ 23 kg/m^2), physical activity (5 years ago, tertiles, MET-hours/week,), total energy intake (kcal/day, quintiles), parity (continuous), oral contraceptive use (never, ever), hormone replacement therapy (no, yes), menopausal status (pre, post), education (none/primary, secondary, vocational/tertiary), smoking status (never, ever), alcohol drinking (no, yes), and family history of ovarian or breast cancer (no, yes).

[b] Sum of fresh tofu and dried tofu due to small quantities consumed for the latter