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Soy and Isoflavone Intake Are Associated With Reduced Risk of Ovarian Cancer in Southeast China

Min Zhang, Xing Xie, Andy H. Lee, and Colin W. Binns

Abstract: *To investigate whether intake of soy and isoflavones has an inverse association with ovarian cancer risk, a case-control study was conducted in Hangzhou, China. Cases were 254 patients with histologically confirmed epithelial ovarian cancer. The 652 controls comprised 340 hospital visitors, 261 non-neoplastic hospital outpatients, and 51 women recruited from the community. Habitual dietary intakes including 9 soy foods were measured by face-to-face interview using a validated and reliable food-frequency questionnaire. Unconditional logistic regression analyses were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) accounting for age, demographic characteristics, hormonal factors, and total energy intake. Intake of soy and isoflavones was inversely related to the risk of ovarian cancer. Compared with the highest versus the lowest quartile intake, the ORs were 0.50 (95% CI = 0.31–0.82) for total soy foods and 0.51 (95% CI = 0.31–0.85) for isoflavones. Among subgroups of soy foods and isoflavones, the ORs for soybeans, bean curd, daidzein, genistein, and glycitein were 0.35 (95% CI = 0.22–0.58), 0.49 (95% CI = 0.29–0.81), 0.52 (95% CI = 0.31–0.87), 0.50 (95% CI = 0.30–0.84), and 0.59 (95% CI = 0.35–0.97), respectively.*

Introduction

Ovarian cancer is the second most common gynecological cancer and the leading cause of mortality among gynecological malignancies (1). The incidence of ovarian cancer varies from country to country, with the highest rates reported in Western countries and lower rates observed in Asian countries (2). Compared with Western countries, China has a relatively low incidence of about 3.2 per 100,000 women (3), which is about one quarter of the incidence in Europe (13.9 per 100,000 women) (4). These differences in ovarian cancer incidence have suggested that the westernization of lifestyle and diet may play a role in ovarian cancer etiology (5).

Little is known regarding the etiology of ovarian cancer. Previously identified risk factors have been related to hormonal factors. Reduced ovarian cancer risks are associated with oral contraceptive use and fewer menstrual cycles (6), whereas increased risks are associated with infertility, low parity, and hormone replacement therapy (7). Ecological studies have suggested soy consumption as a potential protective factor because dietary intakes of soy products are high in many low-risk countries, and soy is a rich source of phytoestrogens (8,9). Moreover, epidemiological evidence has shown that soy and isoflavone intakes are associated with lower risk of various hormone-related cancers, including breast, prostate, and endometrial cancers (10–12). Soy is widely consumed in China and is a primary source of isoflavones. This study investigates whether the intake of soy and isoflavones has an inverse association with the risk of epithelial ovarian cancer, which accounts for more than 90% of all ovarian malignancies (13).

Materials and Methods

Study Design and Participants

A case-control study was conducted in Hangzhou, China, between July 1999 and June 2000. Cases were women under 75 yr, who had been residents of Zhejiang province for at least 10 yr, with a histopathological diagnosis of epithelial ovarian cancer within the past 3 yr. To ensure complete ascertainment of cases, all medical records and laboratory pathology reports were screened daily during the study period. Reports based on pathology specimens and blood samples were also collected for further confirmation of diagnosis. A total of 255 cases were identified, and only 1 patient did not participate in the study (nonresponse rate = 0.4%). Most of the cases (191 patients, 75.2%) were recent patients recruited within 12 mo from diagnosis.

During the same period, 652 controls were recruited and interviewed. Controls were women with neither a neoplasm nor bilateral oophorectomy. Women recruited for controls

M. Zhang, A. H. Lee, and C. W. Binns are affiliated with the School of Public Health, Curtin University of Technology, Perth, WA, Australia. M. Zhang is also affiliated with the School of Population Health, The University of Western Australia, Perth, WA, Australia. X. Xie is affiliated with the Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

were matched with cases by age (within 5 yr). The control group consisted of 340 hospital visitors (15 women declined to be interviewed, nonresponse rate = 4.4%), 261 outpatients (nonresponse rate = 1.2%) recruited from the same hospitals where the cases were identified, and 51 women (nonresponse rate = 7.8%) recruited from the community. To control for bias in selecting the hospital controls, a table of random numbers was used for selecting consulting rooms for outpatients and wards for hospital visitors. These locations were then visited, and outpatients or hospital visitors meeting the selection criteria were interviewed. If no suitable subjects were found in the chosen room/ward, the adjacent room/ward was used instead. This systematic selection process was adopted throughout the entire recruitment period. All the outpatients recruited had only minor gynecological diseases (84.7% had vulvitis, vaginitis, or cervicitis; 6.5% were diagnosed with urethritis; and 5.7% had menopausal symptoms) from gynecological clinics. To evaluate potential hospital bias, another group of community controls was recruited from 9 districts of Hangzhou with assistance from local community councils. These 51 community women were recruited by curbside sampling and interviewed at their homes, community areas near their homes, or their workplaces. The selection criteria for community controls were the same as those for hospital controls. The project was approved by the Chinese hospital authorities and the human research ethics committee of the investigators' institution.

Measurement of Soy Foods Intake

Interviews were conducted using a standard questionnaire that included demographic characteristics, weight and height, habitual dietary intake, physical activity, lifestyle factors, menstrual and reproductive events, hormone use and other factors relevant to hormonal status, and family cancer history. The questionnaire was administered face to face to the subjects after obtaining their formal consent. The interviews usually took between 40 and 50 min.

Habitual dietary intake was assessed using a 128-food item food-frequency questionnaire (FFQ). This quantitative FFQ was adapted from a dietary questionnaire used for studying cancers in Shanghai (14). Additional questions were taken from the Hawaii Cancer Research Survey (15) and the Australian Health Survey 1995 (16). The questionnaire was translated into Chinese and checked (back-translated) by 3 professional Chinese translators.

Usual soy intake was measured by 9 foods that are rich in soy (dry soybean, fresh green soybean, bean curd, dried or pressed bean curd, fried bean curd, fermented bean curd, soybean milk, skin of soybean milk, and soybean sprouts). The frequency of food intake was categorized into never or hardly ever, once a month, 2 or 3 times a month, once a week, 2 or 3 times a week, 4 to 6 times a week, once a day, and at least 2 times a day. Information was also sought on the usual amount of each food consumed per meal as well as cooking methods used and vitamins or mineral supplements taken. The quantitative variables were measured in terms of the Chinese common measure *liang* (equivalent to 50 g). To increase the accuracy of measurement, standard containers (small, 200-ml; medium, 400-ml; and large, 600-ml bowls and a 350-ml cup) were displayed during the interview. Food consumption was based on habitual diet, and a "reference" recall period was set as 5 yr prior to diagnosis (cases) or interview (controls).

The validity and reliability of the FFQ were assessed in a preliminary study and then evaluated by a test–retest. The questionnaire was first pretested on 51 adult Chinese women who recently migrated to Perth, Australia, to assess the feasibility, face, and content validity. Feedback from the participants indicated that they could answer the questions without difficulty, confirming the validity and the successful translation of the questionnaire into Mandarin accounting for the Chinese lifestyle. Because Chinese women are typically responsible for buying food and cooking for the household, the participants could reasonably provide information on the frequency and quantity of each food consumed per meal, using reference containers to estimate the weight of food items. Another test–retest study was then undertaken to assess the reliability of the questionnaire. Forty-one women in Hangzhou were interviewed twice within 11 wk (SD = 6 wk). Intraclass correlations were 0.75, 0.68, 0.85, and 0.65 for mean daily intake of total soy foods, soybeans, bean curd, and other soy foods, respectively. No significant difference was found in mean daily intake of total soy foods as well as the subgroups between the 2 interviews. The high intraclass correlations further supported the reproducibility of the questionnaire.

Data Management and Analysis

All data were checked at the end of each interview for completeness before being coded and analyzed using the SPSS package (17). The daily intake of soy foods (in grams) was obtained based on the variables of frequency and quantity derived from the FFQ, accounting for the edible portion of each food, cooking methods used, seasonal factors, and market availability (18). Daily intakes (in milligrams) of daidzein, genistein, glycitein, and total isoflavones were then estimated based on the soy foods intake using a USDA nutrient database, which had been developed specifically for Chinese immigrants in America (19). The mean daily intakes of soy foods and isoflavone were tabulated separately for case and control groups. To control for hospital bias, data from the 3 control groups were initially compared to assess for potential differences. Because there was no difference among them, the control groups were then combined prior to comparison with the cases. To minimize survival bias, data for the 191 incidence patients and data for all cases were analyzed separately.

Demographic characteristics and potential risk factors between cases and controls were compared using *t*-test for continuous variables and χ^2 test for categorical variables. Following a previous study of prostate cancer in China (11), the 9 soy foods were classified into total soy foods consumption (all 9 foods) and 3 subgroups: soybeans (dry soybean plus fresh green soybean), bean curd, and other soy foods (dried or pressed bean curd, fried bean curd, fermented bean curd, soybean milk, skin of soybean milk, and soybean sprouts).

Variables were divided into quartiles based on the corresponding empirical distribution of controls, with the lowest quartile being the reference category. Odds ratios (ORs) and associated 95% confidence intervals (CIs) associated with the quartile intake of soy foods and isoflavones were computed using unconditional multivariate logistic regression models. Each fitted regression equation adjusted for age at diagnosis (years), education (none, primary, secondary, tertiary), area of residence (urban, rural), body mass index (BMI), tobacco smoking (never, ever), alcohol consumption (never, ever), tea drinking (never, ever), physical activity (weekly MET-hour), age at menarche (years), parity (full-term pregnancy), menopause status (no, yes), hormone replacement therapy (never, ever), oral contraceptive use (never, ever), family history of ovarian cancer (no, yes), and total energy intake (kilocalories). The quantities for the intake of soy foods and isoflavones were tested for linear trend in terms of ovarian cancer risk.

Results

The community controls were first compared with the hospital controls. Although community controls reported a higher consumption of other soy foods, there were no significant differences between hospital and community controls in terms of mean daily intake of soybeans, bean curd, total isoflavones, daidzein, genistein, and glycitein. Data from all 3 control groups were therefore combined to form a single control group to increase the sample size for subsequent analyses. Results from recent patients and all cases were also similar. Therefore, we report the combined results of all cases.

Table 1 shows selected characteristics of cancer cases and controls. There were no differences in mean age, area of residence, BMI (5 yr ago), smoking, alcohol consumption, age at menarche, menopausal status, and hormone replacement therapy between cases and controls. Compared with controls, patients with epithelial ovarian cancer tended to have a higher education, lower parity, less frequent oral contraceptive use and physical activity, and lower energy intake and drank less tea. Most of them had apparent family susceptibility.

Table 2 summarizes the mean daily intake of soy foods and isoflavones by case and control groups. Except for the subgroup of "other soy foods," intakes of soy foods and isoflavones were significantly lower in ovarian cancer cases than in controls.

Table 3 presents the adjusted ORs and 95% CIs of epithelial ovarian cancer risk according to quartile intake of soy foods and isoflavones. A substantial reduction in ovarian cancer risk was evident for the highest versus the lowest quartile of daily intake of total soy foods (OR = 0.50; 95% CI = 0.31–0.82) and total isoflavones (OR = 0.51; 95% CI = 0.31–0.85). Among the subgroups of soy foods, the adjusted ORs were 0.35 (95% CI = 0.22–0.58) for soybeans, 0.49 (95% CI = 0.29–0.81) for bean curd, and 0.57 (95% CI = 0.35–0.97) for other soy foods intake. Among the subgroups of isoflavones, the adjusted ORs were 0.52 (95% CI = 0.31–0.87) for daidzein, 0.50 (95% CI = 0.30–0.84) for genistein, and 0.59 (95% CI = 0.35–0.97) for glycitein. The corresponding linear trends were also significant except for the subgroup of other soy foods. Finally, adjustment for other confounding variables such as dietary fiber and vegetable and fruit consumption in the models had little impact on the results (data not shown).

Discussion

This study of Chinese women, a population with high consumption of soy foods, is the first report to confirm that higher intakes of soy foods and isoflavones can reduce ovarian cancer risk. The new finding is consistent with previous ecological and experimental studies (8,9).

Ovarian cancer is an estrogen-dependent cancer (20). Experimental studies have provided plausible mechanisms for the protective effect of soy foods and isoflavones against ovarian cancer. Estrogens found in plant foods (that is, phytoestrogens), such as isoflavones present in soybeans, have been shown to lower endogenous estrogen levels (21,22). Soybean phytoestrogens also stimulate the production of sex hormone-binding globulin by the liver, which in turn leads to more bound and less free estradiol, reducing the amount of estrogens available for binding with estrogen receptors (23,24). Because of their weak estrogenic potential (>1,000 times lower that estradiol), soybean phytoestrogens do not elicit a strong estrogenic response and thus have an anti-estrogenic effect that inhibits the growth and proliferation of estrogen-dependent cancer cells (25). A recent randomized controlled trial reported that increased isoflavone intake can affect estrogen metabolism by altering the steroid hormone concentrations and menstrual cycle length (26).

Several issues should be considered when interpreting the findings. Extensive information on soy foods intake and dietary patterns was obtained using a validated and reliable instrument specifically developed for the adult Chinese population. In the preliminary test, face validity and content validity of the FFQ were verified. In a subsequent test–retest, the intraclass correlation ranged between 0.65 and 0.85 for mean daily intake of soy foods, confirming the reproducibility of the FFQ to measure usual soy intake. Mean intake of total soy foods in the study subjects (83.2 g/day for cases and 107.5 g/day for controls) was comparable with that previously reported for Chinese men (11). It has been reported that high soy intake during adolescence may reduce the risk of breast cancer in later life (27). In this study, questions on dietary intakes related to the usual diet during adulthood. It may be assumed, however, that the soy food consumption pattern is similar to that of childhood and adolescence for the target population of Chinese women because eating patterns evolve over a period of many years (27,28).

Table 1. Selected Characteristics of Cancer Cases and Controls[a]

	Cases (n = 254) No. (%)	Controls (n = 652) No. (%)	P^b
Age at diagnosis (yr): mean (SD)	46.8 (12.5)	48.0 (10.2)	0.14
<45	128 (41.4)	215 (33.0)	
45–54	110 (35.6)	290 (44.5)	
55–64	48 (15.5)	108 (16.6)	
≥65	23 (7.4)	39 (6.0)	
Education			0.04
None	44 (17.3)	133 (20.4)	
Primary	73 (28.7)	216 (33.1)	
Secondary	95 (37.5)	230 (35.3)	
Tertiary	42 (16.5)	73 (11.2)	
Area of residence			0.28
Urban	148 (58.3)	354 (54.3)	
Rural	106 (41.7)	298 (45.7)	
Body mass index (kg/m²)			0.16
≤25	206 (81.1)	554 (85.0)	
>25	48 (18.9)	98 (15.0)	
Tobacco smoking			0.50
Never	249 (98.0)	634 (97.2)	
Ever	5 (2.0)	18 (2.8)	
Alcohol consumption			0.23
Never	197 (77.6)	452 (69.5)	
Ever	57 (22.4)	198 (30.5)	
Tea drinking			<0.001
Never	113 (44.5)	166 (25.5)	
Ever	141 (55.5)	486 (74.5)	
Total daily energy intake (kilocalories): mean (SD)	2,214.8 (585.4)	2,344.5 (599.8)	0.002
Physical activity (weekly MET-hour)			<0.001
Low (<110)	128 (50.4)	247 (37.9)	
Medium (110–140)	80 (31.5)	210 (32.2)	
High (>140)	46 (18.1)	195 (29.9)	
Age at menarche			0.36
<14	27 (10.7)	52 (8.0	
14–15	78 (30.8)	179 (27.5)	
16–17	98 (38.7)	279 (42.9)	
>17	50 (19.8)	140 (21.5)	
No. of delivery of full-term pregnancy			0.03
0	35 (13.8)	42 (6.50)	
1	86 (33.9)	220 (33.8)	
2	77 (30.3)	233 (35.8)	
≥3	56 (22.0)	155 (23.8)	
Menopausal status			0.67
No	150 (59.1)	394 (60.4)	
Yes	104 (40.9)	256 (39.6)	
Hormone replacement therapy			0.15
Never	248 (97.6)	643 (98.9)	
Ever	6 (2.4)	7 (1.1)	
Oral contraceptive use			<0.001
Never	198 (78.0)	416 (64.0)	
Ever	56 (22.0)	234 (36.0)	
Ovarian cancer in first-degree relatives			0.001
No	248 (97.6)	649 (99.8)	
Yes	6 (2.4)	1 (0.2)	

a: Data missing for 2 controls on alcohol consumption, age at menarche, parity, menopausal status, hormone replacement therapy, oral contraceptive use, and ovarian cancer in first-degree relatives.

b: Differences between cases and controls assessed using χ^2 test for categorical variables and t-test for continuous variable.

Another feature of the study was the adjustment of caloric intake and confounders such as physical activity and tea consumption; the latter were shown to be protective factors against ovarian cancer (29,30). Total energy intakes by the controls, as derived from the FFQ, were comparable with data for Zhejiang residents (31), despite the cases reporting a lower caloric intake (2,215 kcal/day) than the controls (2,344 kcal/day). Furthermore, the bioavailability of self-reported usual intake of soy isoflavones as determined from the FFQ has been documented in the literature. There were strong correlations among plasma concentrations, urinary excretion of isoflavones, and self-reported soy intake (32–34), suggesting

Table 2. Mean Daily Intake of Soy Foods and Isoflavones by Cases and Controls

Daily Intake	Cases (n = 254)Mean (SD)	Controls (n = 652)Mean (SD)	P^a
Total soy foods (g)	83.2 (71.1)	107.5 (93.1)	<0.001
Soybeans	13.4 (13.0)	18.2 (14.3)	<0.001
Bean curd	28.2 (28.6)	38.2 (37.3)	<0.001
Other soy foods	41.6 (59.0)	51.0 (73.4)	0.07
Total isoflavones (mg)	19.2 (13.3)	24.7 (18.8)	<0.001
Daidzein	8.6 (6.0)	11.0 (8.5)	<0.001
Genistein	11.8 (8.4)	15.1 (11.7)	<0.001
Glycitein	1.0 (0.8)	1.3 (1.1)	<0.001

a: Differences between cases and controls assessed using *t*-test.

Table 3. Adjusted ORs[a] and 95% CIs of Epithelial Ovarian Cancer Risk for Quartile Intake of Soy Foods and Isoflavones

	Quartiles[b]				
Daily Intake	Q1	Q2	Q3	Q4	χ_1^2 for Trend
Total soy foods (g)	≤47.0	47.1–81.5	81.6–136.3	≥136.4	
No. cases/controls	86/163	76/163	49/163	43/163	
OR	1.0	0.86	0.61	0.50	11.91
95% CI		0.57–1.31	0.38–0.96	0.31–0.82	(P = 0.001)
Soybeans (g)	≤8.9	8.91–13.3	13.36–26.3	≥26.4	
No. cases/controls	119/181	50/157	55/151	30/163	
OR	1.0	0.52	0.62	0.35	10.39
95% CI		0.34–0.80	0.41–0.94	0.22–0.58	(P = 0.001)
Bean curd (g)	≤10.0	10.1–25.0	25.1–45.0	≥45.1	
No. cases/controls	68/129	80/176	66/185	40/162	
OR	1.0	0.83	0.75	0.49	13.07
95% CI		0.54–1.29	0.48–1.17	0.29–0.81	(P < 0.001)
Other soy foods (g)	≤11.2	11.3–24.6	24.7–57.2	≥57.3	
No. cases/controls	78/163	60/163	71/163	45/163	
OR	1.0	0.76	0.91	0.57	2.13
95% CI		0.49–1.18	0.59–1.42	0.35–0.94	(P = 0.15)
Total isoflavones (mg)	≤11.6	11.7–20.4	20.5–32.7	≥32.8	
No. cases/controls	81/163	76/163	59/163	38/163	
OR	1.0	0.83	0.74	0.51	13.19
95% CI		0.55–1.27	0.47–1.15	0.31–0.85	(P < 0.001)
Daidzein (mg)	≤5.0	5.1–8.8	8.9–14.8	≥14.9	
No. cases/controls	80/163	74/163	60/163	40/163	
OR	1.0	0.82	0.74	0.52	12.37
95% CI		0.54–1.26	0.48–1.16	0.31–0.87	(P << 0.001)
Genistein (mg)	≤6.6	6.7 – 12.1	12.2 –20.8	≥20.9	
No. cases/controls	82/163	70/163	61/163	41/163	
OR	1.0	0.72	0.75	0.50	12.46
95% CI		0.47–1.10	0.48–1.16	0.30–0.84	(P << 0.001)
Glycitein (mg)	≤0.4	0.5–1.0	1.1–1.6	≥1.7	
No. cases/controls	76/163	74/163	63/163	41/163	
OR	1.0	0.98	0.91	0.59	9.99
95% CI		0.64–1.50	0.58–1.42	0.35–0.97	(P = 0.002)

a: Estimates from multivariate logistic regression models included terms for age at diagnosis (years), education, area of residence, body mass index, tobacco smoking, alcohol consumption, tea drinking, physical activity (weekly MET-hour), age at menarche (years), parity, menopausal status, hormone replacement therapy, oral contraceptive use, ovarian cancer in first-degree relatives, and total energy intake (kilocalories).
b: Reference category is the first quartile; quartiles are derived from the distribution of controls.

that the usual soy intake by participants and isoflavone estimates as derived from the FFQ should be reasonably reliable for subsequent analysis.

As far as potential sources of biases are concerned, selection bias appeared to be minimal in view of the low refusal rate and our systematic recruitment procedure. The study attracted participation from most (99.6%) ovarian patients. Hospital records were reviewed daily and all cases had been accounted for. The majority of cases were recently diagnosed, and the recruitment and identification procedures ensured that ascertainment of cases was maximized and complete. For the hospital control sample, it is possible that their recorded dietary practices may not be representative of those of the female population in Zhejiang province. However, we interviewed another sample of community women and found the mean intakes of soy foods were similar between community and hospital controls. Although community controls reported a higher consumption of 'other soy foods,' the intakes of soybeans, bean curd, total isoflavones, daidzein, genistein, and glycitein were similar between the 2 groups. Moreover, the exclusion of community controls did not affect the findings of this study. Recall error was minimized by reporting habitual dietary intake and by using a "reference" recall period. Given the lack of knowledge by the participants on the role of soy foods and isoflavones in ovarian cancer and their blindness to the purpose of the study, information bias in their responses is unlikely. In conclusion, this study suggests that higher intake of soy foods and isoflavones can offer protection against ovarian cancer.

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Address correspondence to M. Zhang, School of Population Health, The University of Western Australia, 35 Stirling Highway, Crawley, WA 6009, Australia. Phone: 61-8-6488 8175. FAX: 61-8-6488 1188. E-mail: minzhang@sph.uwa.edu.au.

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