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Interaction of soy and *17β-HSD1* gene polymorphisms in the risk of endometrial cancer

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Abstract

Background—In-vitro studies have found that soy isoflavones can inhibit the activity of 17β-hydroxysteroid dehydrogenase type I, a key enzyme in catalyzing estrone (E1), to the biologically more active estradiol (E2).

Objective—We hypothesized that soy food consumption may interact with polymorphisms in the *17β-HSD1* gene in the development of endometrial cancer and evaluated this hypothesis in the Shanghai Endometrial Cancer Study.

Methods—Shanghai Endometrial Cancer Study is a population-based case–control study conducted among Chinese women in Shanghai. This study consisted of 1204 incident endometrial cancer cases diagnosed between 30 and 69 years of age and 1212 age frequency-matched community controls recruited from 1997 to 2003. Overall participation rates were 82.8% for cases and 74.4% for controls, whereas the DNA collection rates were 95.1% for cases and 94.2% for controls.

Results—We found that women carrying at least one A allele of the rs605059 polymorphism had a significant 18% reduction in risk of endometrial cancer compared with those without an A allele, and the association was primarily restricted to premenopausal women. The odds ratio (95% confidence interval) was 0.65 (0.47–0.88) for premenopausal women with at least one A allele versus those without an A allele. We also found that among premenopausal women soy isoflavone intake significantly interacted with the rs605059 genotype in relation to endometrial cancer and that the inverse association between soy isoflavone intake and endometrial cancer only appeared among those with at least one A allele of the rs605059 polymorphism. Among postmenopausal women, the association of soy isoflavone intake with endometrial cancer did not differ by *17β-HSD1* genotypes. We did not find that the rs2676530 polymorphism was significantly associated with endometrial cancer risk.

Conclusions—Our results suggest that soy consumption may interact with polymorphisms in the *17β-HSD1* gene in relation to endometrial cancer risk. Further studies are warranted to confirm our results.

Keywords

17β-hydroxysteroid dehydrogenase type I gene; endometrial cancer; soy

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Introduction

The incidence rate of endometrial cancer among women in Asian countries, such as China, is substantially lower than that of their counterparts in Western societies, and the incidence has been found to increase when Asian women migrate to the US [1]. One possible explanation is that lifestyle factors, such as soy foods, consumed in high quantities by Asian women, may confer some protection [2,3]. In the Shanghai Endometrial Cancer Study (SECS), a population-based case–control study conducted among Chinese women in Shanghai, we found that regular intake of soy foods is associated with a reduced risk of endometrial cancer [4]. Evidence from many in-vitro and in-vivo observations suggest that soy foods and their constituents, isoflavones, may reduce endometrial cancer risk by interfering with the synthesis, metabolism, and signal transduction of steroid hormones [2]. Several in-vitro studies have consistently found that isoflavones inhibit 17β-hydroxysteroid dehydrogenase type I (17β-HSD1) activity [2,5], the key enzyme in the last step of estrogen synthesis, catalyzing estrone (E1) to the biologically more active estradiol (E2) in steroidogenic or estrogen-susceptible tissues [6]. We, therefore, hypothesized that soy foods may interact with 17β-HSD1 in the pathogenesis of endometrial cancer and tested this hypothesis using SECS samples to evaluate whether the association of soy food intake with endometrial cancer risk may be modified by two common polymorphisms [rs605059 (Ser312Gly) and rs2676530] in the *17β-HSD1* gene.

Methods

Included in this study were study participants of the SECS [4]. In brief, this study consisted of 1204 incident endometrial cancer cases diagnosed between 30 and 69 years of age and 1212 age frequency-matched community controls recruited from 1997 to 2003. Cancer patients were identified through the population-based Shanghai Cancer Registry that has virtually complete ascertainment of all incident cases diagnosed among residents of urban Shanghai [1,7]. A total of 1454 eligible endometrial cancer patients were identified during the study period, of which 1204 patients (82.8%) completed in-person interviews. All of the patients were confirmed either by histopathology or by medical chart review. The median interval between diagnosis and interview for cases was 5.6 months. Controls were randomly selected from the general population in Shanghai using the Shanghai Resident Registry, a population registry containing demographic information for all residents of urban Shanghai and matched to cases according to the age distribution of endometrial cancer cases in 1996. Women with a history of cancer or hysterectomy were not eligible. Of the 1629 eligible women, 1212 (74.4%) completed in-person interviews. The study was approved by the relevant committees for the use of human subjects in research and written informed consent was obtained from all study participants.

Study participants were interviewed in person by trained nurses and physicians. A structured questionnaire was used to elicit detailed information on demographic factors, menstrual and reproductive history, hormone use, prior disease history, physical activity, tobacco and alcohol use, weight, family history of cancer, and dietary habits, including usual soy food intake. In a validation study, the intake level of soy foods derived from the food frequency questionnaire used in the SECS was correlated well with that derived from multiple 24-h dietary recalls (r = 0.49, $P < 0.001$) [8]. All study participants were measured for their current weight and circumferences of the waist and hips. Of those who completed the in-person interviews, 860 cases and 861 controls donated a blood sample and 285 cases and 281 controls provided a buccal cell sample. Consequently, the DNA collection rate was 95.1% for cases and 94.2% for controls. These samples were processed on the same day, typically within 6 h of sample collection, and were stored at −70°C until relevant bioassays were performed.

Genomic DNA was extracted from buffy coat fractions or buccal cells using a QIAamp DNA mini kit (Qiagen Inc., Valencia, California, USA) as per the manufacturer’s protocol. The

allelic discrimination of the two *17β-HSD1* gene polymorphisms were assessed using TaqMan genotyping assays (C_2350902_10 for rs605059 and C_11626736-20 for rs2676530) on the ABI PRISM 7900 Sequence Detection Systems (Applied Biosystems, Foster City, California, USA). The final volume for each reaction was 5 μl, consisting of 2.5 μl TaqMan Universal PCR Master Mix (Applied Biosystems), 900 nmol/l of each primer, 200 nmol/l of each TaqMan probe, and 5.0 ng genomic DNA. The polymerase chain reaction profile consisted of an initial denaturation step at 95°C for 10 min and 50 cycles with 95°C for 15 s and 60°C for 1 min. The fluorescence level was measured with the ABI PRISM 7900HT sequence detector (Applied Biosystems). Genotypes were determined by Applied Biosystems SDS software.

The laboratory staff was blind to the identity of the study participants. Quality control (QC) samples were included in the genotyping assays. Each 96-well plate contained one water blank, two CEPH 1347-02 DNA, two blinded QC samples, and two unblinded QC samples. The blinded and unblinded QC samples were taken from the second tube of study samples included in the study. QC samples were distributed across separate 96-well plates. The agreement rate for the rs605059 polymorphism with the duplicated QC samples was 97.9 and 100% for rs2676530. Among those who provided a DNA sample, genotyping data were obtained from 1031 (90.0%) cases and 1019 (89.2%) controls for rs605059 (A312G) and 1029 (89.9%) cases and 1015 (88.9%) controls for rs2676530. The major reasons for incomplete genotyping were insufficient DNA used for the assay and unsuccessful polymerase chain reaction amplification.

Estimates of daily intake of soy protein and soy isoflavones were derived using the Chinese food composition tables (Institute of Nutrition and Food Safety, China CDC, 2002). χ^2 statistics were used to evaluate case–control differences in the distribution of genotypes. Multivariate analyses were performed to adjust for potential confounding variables. Logistic regression models were used to estimate odds ratios (ORs) and their 95% confidence intervals (95% CIs) to measure the strength of the association. The linkage disequilibrium between the two polymorphisms was examined using GOLD software (Ann Arbor, Michigan, USA)[9]. Stratified and joint association analyses were performed to evaluate whether the *17β-HSD1* genotype modified the association of soy and menopausal status with endometrial cancer risk. The likelihood ratio test was conducted to formally test multiplicative interactions. In comparison, we also investigated whether the association between the *17β-HSD1* genotypes and endometrial cancer risk may differ by factors related to endogenous and exogenous sex hormones, such as body mass index (BMI), waist-to-hip ratio, and oral contraceptive use. *P* values of less than 0.05 (two-sided probability) were interpreted as statistically significant.

Results

Selected demographic characteristics and major risk factors were compared between cases and controls as shown in Table 1. Cases and controls were similar in age. No significant differences were found between cases and controls with respect to the use of hormone replacement therapy (HRT) or intake of fruits and vegetables. Compared with controls, patients were slightly younger at menarche and older at menopause. Compared with controls, patients were more likely to have higher educational achievement, BMI and waist-to-hip ratio, to have a family history of cancer, to have fewer live births, to consume more total energy, meat, and fish, and were less likely to be physically active or to use oral contraceptives. Therefore, all these significant variables and age were adjusted for in subsequent analyses as potential confounders. No appreciable difference was found between cases included in the genotyping study and those included in the whole study (data not shown).

The allele and genotype distributions for the two common polymorphisms in the *17β-HSD1* gene are presented in Table 2. The distribution of genotypes for these two polymorphisms was consistent with Hardy–Weinberg equilibrium and the *P* value was 0.70 for rs605059 and 0.64

for rs2676530 among controls. The frequency of the A allele for the rs2676530 polymorphism was rare (2.5%). For the rs605059 polymorphism, the GG genotype was twice as prevalent as AA. Overall, risk of endometrial cancer did not vary significantly by rs2676530 polymorphism. For the rs605059 polymorphism, women who possessed at least one A allele were significantly associated with an approximate 20% reduced risk of endometrial cancer compared with those with the GG genotype; stratified analyses by menopausal status showed that the decreased risk associated with the A allele primarily appeared in premenopausal women, with an OR (95% CI) of 0.65 (0.47–0.88) for those carrying at least one A allele versus those with the GG genotype. These two polymorphisms were in close linkage disequilibrium with a Lewontin's D' value of 1.000. The A allele of rs2676530 always appeared with the A allele of rs605059. Consequently, premenopausal women with the A allele of rs2676530 also tended to be at a lower risk for endometrial cancer, although the link was not statistically significant. Soy intake did not appear to vary by genotype in controls. Among controls, the mean intake of soy protein were 11.1 g/day for those with the GG genotype and 10.6 g/day for those with the AG or AA genotype (*P* for *t*-test, 0.28); the mean intake of soy isoflavones were 36.8 mg/day for those with the GG genotype and 35.3 g/day for those with the AG or AA genotype (*P* for *t*-test, 0.36).

Presented in Table 3 are joint associations of soy isoflavone or protein intake and rs605059 (Ser312Gly) polymorphism in association with endometrial cancer risk stratified by menopausal status. For premenopausal women, the risk of endometrial cancer only significantly decreased with increasing soy isoflavone or protein intake for those who carried at least one A allele. Among the women with at least one A allele, the risk of endometrial cancer was reduced 60% for those whose intake of soy isoflavones was in the top tertile (OR = 0.40, 95% CI: 0.22–0.74) versus those whose intake of soy isoflavones was in the bottom tertile. Testing for multiplicative interaction treating intake of soy isoflavones or soy protein as continuous variables, and the genotype of the rs605059 polymorphism (GG versus AG and AA) as dummy variables showed significant interaction (*P* for interaction, 0.03) for soy isoflavones only; the interaction between genotype and soy protein intake failed to reach statistical significance. For postmenopausal women, the association between soy isoflavone or protein intake and endometrial cancer did not differ by the rs605059 genotype. We found among postmenopausal women who used HRT, the ORs were 0.31 (0.07–1.41) and 0.25 (0.05–1.39) for women with the AG or AA genotypes, respectively, compared with women with the GG genotype (*P* for trend, 0.08); and the corresponding ORs were 0.93 (0.70–1.24) and 1.11 (0.77–1.60) among women who did not use HRT (*P* for trend, 0.69). The test for multiplicative interaction, however, was not statistically significant (*P* for interaction, 0.20), probably owing to the low prevalence of HRT use in our study population. We did not find the association between *17β-HSD1* gene polymorphisms and endometrial cancer to differ by factors that would influence endogenous and exogenous sex hormones, such as oral contraceptive use, BMI or waist-to-hip ratio (data not shown).

Discussion

We found in this population-based case–control study that premenopausal women with at least one A allele of the rs605059 (Ser312Gly) polymorphism were at a lower risk for endometrial cancer compared with those without an A allele. Among premenopausal women, we also found that soy isoflavone intake significantly interacted with the rs605059 genotype in relation to endometrial cancer and that the inverse association between soy isoflavone intake and endometrial cancer only appeared among those with at least one A allele of the rs605059 polymorphism. Among postmenopausal women, the association of soy isoflavone or protein intake with endometrial cancer did not differ by the rs605059 polymorphism.

The *17β-HSD1* gene is located on chromosome 17 at region q12–q21. An A→G transition at exon 6 leads to an amino-acid alteration from Ser to Gly at position 312 and this variant is the

only common polymorphism in the coding region of the *17β-HSD1* gene [10]. A site-directed mutagenesis study indicated that this polymorphism might not significantly change either the catalytic or the immunological properties of the enzyme [11]. Nevertheless, several epidemiological studies have found that compared with women with the GG genotype, study participants with at least one A allele were associated with a moderately increased risk of breast cancer [6,12,13]. Likewise, Setiawan *et al.* [14] found in the Nurses' Health Study that women with the AA genotype may also be at an elevated risk of endometrial cancer with an OR of 1.27 (95% CI: 0.80–2.02) versus those with the GG genotype. These epidemiological data indicate that there might be a small reduction in enzyme activity owing to the Ser→Gly alteration that may not be large enough to be detected in functional assays [12]. On the contrary, we found in the current study that women, particularly premenopausal women, who carried at least one A allele had a significantly reduced risk of endometrial cancer. The inconsistency between the result from our study and those from previous studies is unlikely to be due to a genotyping error in our study, as the genotype frequency for the A312G polymorphism in our study is very similar to that in the Shanghai Breast Cancer Study, a large population-based case–control study conducted among the same population during a similar period of time (unpublished results), and in a Chinese population in Singapore [13]. Furthermore, there was very high agreement between the genotyping results and the duplicated QC samples and the distribution of genotypes was consistent with Hardy–Weinberg equilibrium for both cases and controls.

One possible explanation for this inconsistency is that it might be partly attributable to the potential interaction between phytoestrogen intake and the 17β-HSD1 enzyme. A number of in-vitro studies have consistently found that isoflavones inhibit the activity of 17β-HSD1 [2, 5] in converting E1 to E2. In premenopausal women, the estrogen-susceptible tissue/plasma ratio of E2 was 1:1 [15]. After menopause, E1 substitutes for E2 and becomes the major circulating estrogen and the tissue/plasma ratio of E2 could be 10–50:1 in postmenopausal women [15,16]. Expression of the 17β-HSD1 enzyme was detected in the human ovary, placenta, and mammary glands [17], but not in the normal endometrium, endometrial hyperplasia, or endometrioid endometrial carcinoma [18]. Thus, 17β-HSD1 may not play an important role in regulating E2 concentration in the endometrium after menopause. These biological results suggest that inhibiting the 17β-HSD1 enzyme is unlikely to be the mechanism by which soy isoflavones reduce the risk of endometrial cancer among postmenopausal women. This hypothesis is supported by our findings that the association between intake of soy protein and endometrial cancer did not differ by the functional polymorphism in the *17β-HSD1* gene in postmenopausal women. In premenopausal women, on the other hand, soy protein may reduce circulating E2 concentration by inhibiting 17β-HSD1 activity in the ovaries. A number of human intervention trials, although not all [19], have found that high intake of either isoflavones or soy foods reduce blood E2 levels among premenopausal women [20–23]. We found in a previous report that the risk of endometrial cancer was reduced only among those whose daily intake of isoflavones was equal to or greater than 43 mg/day, particularly for those who consumed over 62 mg of isoflavones per day [4]. Interestingly, the intervention trial with a significant finding was also mainly restricted to those with a higher supplementation level of isoflavones (> 100 mg/day) or those using a more potent form of isoflavone (genistein) [20,21,23]. In this study, we also found the interaction with genotype was only significant for soy isoflavones, but not soy protein, indicating that it is the phytoestrogen isoflavones from soy that play a major role. Furthermore, we have found a similar potential interaction between urinary excretion of isoflavonoids or dietary intake of soy foods and the rs2676530 polymorphism in relation to breast cancer risk (unpublished data) in the Shanghai Breast Cancer Study using the same questionnaire as the current study. On the basis of these findings, we further hypothesize that the amino-acid alteration from serine to glycine may lead to a structural change in the 17β-HSD1 binding domain that, in turn, results in a small reduction in enzyme activity in catalyzing E1 to E2, but a substantial loss in enzyme affinity with

phytoestrogens, particularly soy isoflavones. Therefore, soy isoflavones may compete with E1 to bind to 17β-HSD1 enzymes in the ovaries among premenopausal women who possess the 312AA genotype and, thus, reduce their risk of endometrial cancer. This hypothesis, however, needs to be evaluated in future studies.

In our study, we also observed differential associations between the rs605059 polymorphism and endometrial cancer risk by HRT use status among postmenopausal women, although test for multiplicative interaction was not significant. The inverse association between the rs605059 polymorphism and endometrial cancer risk among postmenopausal women who used HRT resembles the finding of soy and *17β-HSD1* interaction seen among premenopausal women. Use of HRT among postmenopausal women may lead to a high estrogen milieu similar to that for premenopausal women. As we discussed earlier, in our study population with a high intake level of soy foods, soy isoflavones may inhibit 17β-HSD1 enzyme in the ovary among premenopausal women. The major component in the most common formula of HRT is E1. After menopause adipose tissue becomes the major site for estrogen synthesis, where 17β-HSD1 catalyzes E1 to the biologically more active E2. A recent study found that blood levels of E2 after HRT use showed a significant positive correlation with BMI in postmenopausal women or bilaterally ovariectomized women [24]. Therefore, it is possible that soy isoflavones may inhibit the conversion from E1 to E2 in adipose tissue among postmenopausal women who used HRTand possessed at least one A allele for the rs605059. Owing to the low frequency of HRTuse in the study population, however, we cannot evaluate this possibility in the current study. Further studies are warranted.

The rs2676530 polymorphism, (G→A) is located at the intron/exon boundary. We found that the A allele frequency of the rs2676530 polymorphism was 2.5% among Chinese women compared with 22.9% for African and 26.3% for Caucasian populations (http://www.hapmap.org/). The A allele of the rs2676530 polymorphism always appeared together with the A allele of the rs605059 polymorphism. Therefore, we found the association between the rs2676530 polymorphism and endometrial cancer was similar to that for the r605059, although it was not statistically significant because of a low allele frequency.

In this population-based study, the participation rate was relatively high (82.8% for cases and 74.4% for controls) and only 5% of study participants did not donate a DNA sample, all of which may reduce the potential selection bias. Furthermore, we found that those study participants with genotyping data were comparable for all major known risk factors and demographic characteristics with all study participants. Recall bias is another concern. We, however, asked study participants to ignore any dietary change over the past year. The median interval between diagnosis and interview for cases was 5.6 months. In addition, recall of soy food intake is unlikely to be related to *17β-HSD1* genotype. Chinese women living in Shanghai have relatively homogeneous ethnic backgrounds; > 98% of them are classified into a single ethnic group (Han Chinese). Therefore, the potential confounding effect of ethnicity for genotyping data is not a major concern. Finally, although we adjusted for many potential confounding factors, we still cannot exclude the possibility that residual confounding or related dietary patterns may partially explain our results. The focus of this study, however, is on the interaction between genotypes and dietary intake of soy isoflavones. Finally, it is possible that our findings are solely owing to chance, particularly in the stratified analyses, although we have a large sample size and found a similar potential interaction in both the current study and the Shanghai Breast Cancer Study.

Further studies are warranted to confirm our results. It is worth noting that the frequency of 312AA is higher in Caucasians than in Asians [6,12]. Therefore, our findings, if confirmed, may have important implications for the development of personalized preventive strategies against endometrial cancer for both Asian and Caucasian populations.

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Table 1

Comparison of cases and controls by selected descriptive characteristics, Shanghai Endometrial Cancer Study, 1997–2003

Subject characteristics	Cases (1041)	Controls (1033)	*P*-value[a]
Age (years), mean ± SD	54.8 ± 8.5	54.9 ± 8.5	0.66
Education, (%)			
Elementary school or below	21.5	22.5	
Middle or high school	64.0	64.7	
College or above	14.5	12.9	0.41
Cancer in first-degree relative (%)	35.6	29.4	< 0.01
Ever used oral contraceptive (%)	18.2	25.1	< 0.01
Ever used hormone replacement therapy (%)	4.7	4.3	0.62
Age at menarche (years)	14.5 ± 1.7	14.8 ± 1.8	< 0.01
Number of pregnancies, mean ± SD	1.7 ± 1.2	1.8 ± 1.1	0.07
Postmenopausal (%)	56.7	61.9	0.02
Age at menopause (years), mean ± SD	50.3 ± 3.6	49.0 ± 3.6	< 0.01
Physically active past 10 years (%)	28.1	33.8	< 0.01
BMI (kg/m^2), mean ± SD	25.7 ± 4.2	23.8 ± 3.5	< 0.01
Waist-to-hip ratio, mean ± SD	0.84 ± 0.05	0.82 ± 0.05	< 0.01
Daily energy intake (kcal), mean ± SD	1803.5 ± 462.4	1758.8 ± 464.8	0.03
Daily intake of total meat (g), mean ± SD	55.3 ± 42.9	49.0 ± 40.5	< 0.01
Daily intake of fruits and vegetables (g), mean ± SD	556.3 ± 314.9	551.8 ± 324.4	0.32
Daily intake of fish (g), mean ± SD	59.3 ± 48.4	49.2 ± 45.2	< 0.01
Daily intake of soy protein (g), mean ± SD	10.4 ± 7.1	10.8 ± 7.8	0.26
Daily intake of soy isoflavones (mg), mean ± SD	34.7 ± 24.3	36.0 ± 25.8	0.24

BMI, body mass index.

[a] For χ^2 test (categorical variables) or *t*-test (continuous variables).

Table 2

17β-HSD1 allele and genotype frequencies, unadjusted and adjusted ORs by menopausal status for endometrial cancer, the Shanghai Endometrial Cancer Study, 1997–2003

17β-HSD1 Genotype[a]	Cases *n* (%)	Controls *n* (%)	*P*-value	OR (95% CI)[b]	OR (95% CI)[c]
rs605059 (Ser312Gly)					
GG	380 (36.9)	358 (35.1)		1.00	1.00
AG/AA	651 (63.1)	661 (64.9)		0.93 (0.77–1.11)	0.82 (0.67–1.00)
AG	465 (45.1)	487 (47.8)		0.90 (0.74–1.09)	0.79 (0.64–0.98)
AA	186 (18.0)	174 (17.1)	0.47	1.01 (0.78–1.30)	0.89 (0.68–1.17)
			P for trend	0.82	0.20
rs2676530 Intron (boundary)					
GG	979 (95.1)	965 (95.1)		1.00	1.00
AG/AA	50 (4.9)	50 (4.9)		0.99 (0.66–1.47)	1.01 (0.65–1.57)
AG	49 (4.8)	49 (4.8)		0.99 (0.66–1.48)	1.02 (0.66–1.60)
AA	1 (0.1)	1 (0.1)	1.00	0.99 (0.06–15.86)	0.37 (0.01–11.25)
			P for trend	0.61	0.97
	Premenopausal women[c]			Postmenopausal women[c]	
rs605059 (Ser312Gly)					
GG	176/133	1.00		204/225	1.00
AG/AA	271/257	0.65 (0.47–0.88)		380/404	0.94 (0.7–1.21)
AG	197/192	0.63 (0.45–0.88)		268/295	0.90 (0.68–1.18)
AA	74/65	0.69 (0.45–1.08)		112/109	1.03 (0.73–1.46)
	P for trend	0.03			0.98
rs2676530					
GG	430/371	1.00		549/594	1.00
AG/AA	18/18	0.69 (0.33–1.46)		32/32	1.24 (0.71–2.16)

ORs, odds ratios; CI, confidence interval.

[a] The frequencies of the A allele of rs605059 were 40.6% in cases and 41.0% in controls ($P = 0.80$), the T allele of rs2676530 polymorphism were 2.5% in cases and 2.5% in controls ($P = 0.94$).

[b] Adjusted for age only.

[c] Adjusted for age, education, menopausal status, use of oral contraceptives, years of menstruation, body mass index, first-degree family history of any cancer, physical activity, number of pregnancies, intake of total meat and fish, soy protein, total energy.

Table 3

Stratified analyses of the association between soy food intake and endometrial cancer risk by *17β-HSD1* genotype, the Shanghai Endometrial Cancer Study, 1997–2003

Variables	Cases/controls	OR(95% CI)[a]	Cases/controls	OR(95% CI)[a]	Cases/controls	OR(95% CI)[a]
Soy isoflavone intake (g/daily)						
		T1 (Low)		T2		T3
Premenopausal women rs605059 (Ser312Gly)						
GG	48/48	1.00 (Reference)	65/38	1.44 (0.78–2.65)	63/47	0.87 (0.47–1.62)
AG/AA	108/85	1.03 (0.61–1.76)	105/94	0.72 (0.42–1.23)	58/78	0.40 (0.22–0.74)
			P for interaction, 0.03			
Postmenopausal women rs605059 (Ser312Gly)						
GG	63/63	1.00 (Reference)	68/84	0.70 (0.42–1.17)	73/78	0.82 (0.48–1.39)
AG/AA	119/132	0.81 (0.51–1.29)	120/126	0.79 (0.50–1.27)	141/146	0.73 (0.45–1.16)
			P for interaction, 0.89			
Soy protein intake (g/daily)						
		T1 (Low)		T2		T3
Premenopausal women rs605059 (Ser312Gly)						
GG	53/47	1.00 (Reference)	61/40	1.04 (0.57–1.91)	62/46	0.78 (0.42–1.46)
AG/AA	101/87	0.78 (0.42–1.46)	109/94	0.61 (0.36–1.03)	61/76	0.40 (0.22–0.73)
			P for interaction, 0.17			
Postmenopausal women rs605059 (Ser312Gly)						
GG	61/63	1.00 (Reference)	69/80	0.80 (0.48–1.35)	74/82	0.79 (0.46–1.33)
AG/AA	125/132	0.89 (0.56–1.42)	114/125	0.82 (0.51–1.32)	141/147	0.70 (0.44–1.13)
			P for interaction, 0.80			

OR, odds ratio; CI, confidence interval.

[a] Adjusted for age, education, menopausal status, use of oral contraceptives, years of menstruation, body mass index, first-degree family history of any cancer, physical activity, number of pregnancies, intake of total meat and fish, total energy.