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Original article

Plasma phytoestrogens concentration and risk of colorectal cancer in two different Asian populations

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SUMMARY

Background & aims: To evaluate the relationship between phytoestrogen and colon cancer risk, we quantified plasma isoflavones (Genistein and Daidzein) and lignan (enterolactone) in a Korean nested case-control study and conducted replication study in a Vietnamese case-control study.

Methods: Study populations of 101 cases and 391 controls were selected from the Korean Multicenter Cancer Cohort which was constructed from 1993 to 2004. For replication study, Vietnamese hospital-based case-control subjects of 222 cases and 206 controls were selected from 2003 to 2007. The concentrations of plasma genistein, daidzein, and enterolactone were quantified by liquid chromatography-mass spectrometry. Logistic regression models were used to compute odds ratios (ORs) and 95% confidence intervals (CIs), and meta-analysis was conducted to estimate combined ORs (CORs) and 95% Cis of Korean and Vietnamese population in 2014.

Results: Genistein showed a continual decrease in colorectal cancer risk according to level up of the concentration categories in Korean and Vietnamese population (P for trend = 0.032, and 0.001, respectively) and a significantly decreased risk was found at the highest concentration of genistein and daidzein (for the highest category compared to the lowest: COR (95% CI) = 0.46 (0.30–0.69), and COR (95% CI) = 0.54 (0.36–0.82)). When the study population was stratified, the beneficial relationship of genistein with colorectal cancer was observed regardless of sex and anatomical subtype. However, enterolacton level was not associated with colorectal cancer risk.

Conclusions: High plasma levels of isoflavones had relationship with a decreased risk of colorectal cancer, regardless of different ethnic background.

Abbreviations: OR, odds ratio; COR, combined odds ratio; CI, confidence interval; FFQ, food-frequency questionnaire; KMCC, Korean Multi-center Cancer Cohort.

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1. Introduction

Colorectal cancer has traditionally been less common in Asian countries compared with Western countries [1]. A higher incidence of colorectal cancer in men compared with women can be seen, and this pattern displays remarkable persistence across populations and over time [2]. This lower rate of the colorectal cancer incidence in women and in Asia suggests that estrogen hormone can have a role in the pathogenic pathway of colorectal cancer and so high consumption of phytoestrogen-contained foods such as soybean products and sesame seeds might attribute for the low incidence of colorectal cancer in Asian population [3,4]. Isoflavones and lignans are major types of phytoestrogen which have similar structure with estrogen [5]. The isoflavones are abundant in soybeans and the lignans are a group of chemical compounds contained in their high levels in flax and sesame seeds and in low levels in cereals [6].

However, epidemiologic studies conducted in China [7] and Japan [8–10] has found that the health benefits of phytoestrogen-contained foods for colorectal cancer are limited and inconsistent. The inconsistent results may be caused partially by the use of food-frequency questionnaires (FFQs) and variation in the exposed quantity. Although FFQs measure typical dietary habits of long-term period relatively, FFQs are prone to information bias, including failure of memory, differential recollection, and misclassification bias [11]. Thus, measuring biomarkers and employing a prospective cohort study design may help in reducing such biases [12].

In the nested case control study in Korean population, we measured phytoestrogen biomarkers (genistein and daidzein for isoflavone level, and enterolactone for lignin level) to assess if phytoestrogens have association with the risk of colorectal cancer. We assessed the reproducibility of the relationship between plasma phytoestrogens and risk of colorectal cancer by conducting a case-control study in a Vietnamese population.

2. Materials and methods

2.1. Study population

For the nested case-control study, eligible subjects were selected from the Korean Multi-center Cancer Cohort (KMCC). The rationale and design of the KMCC was explained in detail elsewhere [13]. Briefly, the KMCC is a prospective cohort study conducted in community. Study participants were recruited voluntarily from 1993 to 2004 from 4 rural and urban areas in Korea. We identified colorectal cancer cases in computerized records (as of December 2008) that were linked to the Korea Central Cancer Registry as well as the National Death Certification databases. We excluded cases with insufficient plasma for laboratory assay and cases that were diagnosed before the recruitment period. We matched four controls to each cancer case according to age (±5 years old), sex, resident area, and recruitment year. Controls were not diagnosed with colorectal cancer and were alive until the diagnosed time of the matched cases. A total of 102 cases and 408 controls were selected.

For a replication study, eligible subjects were selected from hospital patients in Vietnam. Cases were histologically newly diagnosed colorectal cancer patients recruited from 2003 to 2007 in 3 hospitals in Hanoi. Controls were cancer-free patients who were hospitalized for surgery in the same hospital at the same time. Common diseases of controls were injury, urinary tract stone, biliary tract stone, prostate fibroma, and non-cancer operation. Blood samples were stored at minus 70 °C in a deep-freezer. Finally, 222 cases and 206 controls were selected for the replication study.

The study protocol was approved by the research ethics committee at Gachon University and Gil Hospital.

2.2. Measurements

Information was collected through structured questionnaires on demographic factors, reproductive factors, and general life-style such as smoking, alcohol drinking, physical activity, and dietary habit by trained interviewer. For obtaining the anthropometric index, height, weight, and waist circumference were measured.

We used blood samples, which had been stored at deep freezer of −70 °C from the enrollment, to measure the phytoestrogen level. Plasma concentrations of the phytoestrogen such as genistein, daidzein and enterolactone were quantified by liquid chromatography-mass spectrometry for Korean nested case-control study in 2013 and Vietnamese case-control study in 2014. This method permits the high precision, high sensitivity and rapid display of result in spite of small volumes of plasma [14]. Total isoflavone concentration was considered as the sum of genistein and daidzein concentrations.

2.3. Statistical analysis

The student *t*-test and chi-square test was applied to test differences of age and sex between cases and controls. A Wilcoxon rank sum test was applied to compare the median plasma phytoestrogen concentrations between cases and controls in the Korean and Vietnamese samples. To maximize the comparability between cases and controls, the concentration of isoflavones and enterolactone were categorized according to the quartiles within the cases in each population of Korean and Vietnamese, men and women, and colon and rectal cancer.

In the nested case-control study in Korea and the case-control study in Vietnam, multiple logistic regression models were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for colorectal cancer risk by the categorized plasma phytoestrogens levels. Multiple logistic regression models were adjusted for age, sex, smoking, alcohol drinking, body mass index, educated years, vegetable intake and fruit intake which are associated factors of colorectal cancer or effect modifiers of other risk factors. A trend test for *P* value was calculated using a likelihood ratio test. To examine the association between plasma phytoestrogens concentration and risk of colorectal according to sex and anatomical subtype, the stratified analyses were conducted. Meta-analyses were conducted to assess the association between plasma phytoestrogens and colorectal cancer in the Korean and Vietnamese data and combined ORs (CORs) and 95% CI were estimated. Heterogeneity *Q* test was conducted to compare the results in the Korean and Vietnamese data. All analyses were performed using SAS 9.3 in 2014 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Baseline characteristics and plasma concentrations of phytoestrogens

Eighteen samples were failed to measure the plasma phytoestrogen level, and finally 101 colorectal cancer cases and 391 controls were included for the Korean nested case-control study and 222 colorectal cancer cases and 206 controls were included for the case-control study in Vietnam (Table 1). The mean (standard deviation) age of study subjects was 60.2 (9.8) and 60.4 (9.6) in Korean cases and controls and 55.3 (12.7) and 54.5 (14.1) in Vietnamese cases and controls, respectively. There were no differences in smoking history, alcohol drinking, body mass index, education level, and diet frequency of fruit, vegetable, and meat consumption between cases and controls in the Korean nested case-control study (Supplement Table 1).

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Table 1
Baseline characteristics and plasma concentrations of phytoestrogens in Korean and Vietnamese.

Variables	Korean			Vietnamese		
	Cases ($N = 101$)	Controls ($N = 391$)	*P*-value	Cases ($N = 222$)	Controls ($N = 206$)	*P*-value
Age, years, Mean (SD)	60.2 (9.8)	60.4 (9.6)	0.893	55.3 (12.7)	54.5 (14.1)	0.547
Sex, *N* (%)			0.970			0.584
Women	53 (52.5)	206 (52.7)		117 (52.7)	114 (55.3)	
Men	48 (47.5)	185 (47.3)		105 (47.3)	92 (44.7)	
Phytoestrogen (ng/ml), Women						
Genistein, median (IQR)	145.8 (80.7–459.3)	223.5 (126.4–422.7)	0.157	190.2 (87.9–430.4)	328.2 (119.1–1123)	**0.011**
Daidzein, median (IQR)	61.9 (27.4–133.7)	68.9 (32.3–157.2)	0.583	32.8 (5.2–65.9)	43.3 (24.3–172.0)	**0.011**
Enterolactone, median (IQR)	65.6 (28.0–118.6)	74.3 (29.6–162.6)	0.253	2.25 (0.0–9.2)	3.04 (0.0–12.5)	0.804
Phytoestrogen (ng/ml), Men						
Genistein, median (IQR)	185.8 (89.6–363.1)	198.5 (108.0–428.9)	0.576	212.0 (91.3–607.8)	250.7 (141.6–945.2)	**0.047**
Daidzein, median (IQR)	74.0 (25.3–152.6)	71.4 (31.5–172.8)	0.908	30.5 (8.1–62.0)	45.0 (18.6–149.7)	**0.049**
Enterolactone, median (IQR)	58.6 (30.3–116.5)	53.0 (22.8–114.8)	0.672	2.25 (0.0–11.3)	3.1 (0.0–11.3)	0.788

Bold values indicate *P*-value less than 0.05.

In the Korean sample, median concentrations of genistein, diadzein, and enterolactone were not heterogeneous between cases and controls. In the Vietnamese sample, median levels of genistein and daidzein were higher in controls than cases.

3.2. Colorectal cancer risk and plasma concentrations of phytoestrogens

In the Korean sample, a continual decrease was observed in colorectal cancer risk with each additional level of genistein concentration (*P* for trend = 0.032), and a significantly decreased risk was observed at the highest quartile concentration of genistein (for the highest category: OR = 0.50; 95% CI = 0.25–0.98; Table 2). For daidzein, there was no pattern of increased or decreased plasma concentrations associated with colorectal cancer. Total isoflavone was inversely associated with colorectal cancer risk (*P* for trend = 0.043). In the Vietnamese sample, genistein, daidzein, and total isoflavone were associated with a continual decrease in colorectal cancer risk as the concentrations increased (*P* for trend = 0.001, 0.006, and 0.001, respectively); the highest concentration groups were associated with low risks of colorectal cancer (OR = 0.43, 95% CI = 0.25–0.73 for genistein; OR = 0.48, 95%

Table 2
Colorectal cancer risk and plasma concentrations of phytoestrogens in Korean and Vietnamese.

Phytoestrogen (ng/mL)	Korean			Vietnamese			Meta-analysis COR (95% CI)[c]
	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[b]	
	No. (%)	No. (%)		No. (%)	No. (%)		
	$N = 101$	$N = 391$		$N = 222$	$N = 206$		
Isoflavones							
Genistein[d]							
1Q	26 (25.7)	67 (17.1)	1.00 (ref)	56 (25.2)	37 (18.0)	1.00 (ref)	1.00 (ref)
2Q	25 (24.8)	90 (23.0)	0.67 (0.34–1.31)	55 (24.8)	37 (18.0)	0.97 (0.54–1.74)	0.83 (0.53–1.29)
3Q	25 (24.8)	125 (32.0)	0.48 (0.25–0.93)	56 (25.2)	47 (22.8)	0.79 (0.45–1.40)	0.63 (0.39–1.03)
4Q	25 (24.8)	109 (27.9)	0.50 (0.25–0.98)	55 (24.8)	85 (41.3)	0.43 (0.25–0.73)	0.46 (0.30–0.69)
	P for trend		**0.032**			**0.001**	
Daidzein[e]							
1Q	26 (25.7)	82 (21.0)	1.00 (ref)	56 (25.2)	37 (18.0)	1.00 (ref)	1.00 (ref)
2Q	25 (24.8)	104 (26.6)	0.71 (0.36–1.38)	55 (24.8)	43 (20.9)	0.84 (0.47–1.49)	0.78 (0.51–1.21)
3Q	24 (23.8)	90 (23.0)	0.87 (0.44–1.72)	56 (25.2)	50 (24.3)	0.74 (0.42–1.30)	0.79 (0.51–1.22)
4Q	26 (25.7)	115 (29.4)	0.65 (0.33–1.27)	55 (24.8)	76 (36.9)	0.48 (0.28–0.82)	0.54 (0.36–0.82)
	P for trend		0.321			**0.006**	
Total isoflavone[f]							
1Q	26 (25.7)	64 (16.4)	1.00 (ref)	56 (25.2)	34 (16.5)	1.00 (ref)	1.00 (ref)
2Q	25 (24.8)	94 (24.0)	0.60 (0.31–1.17)	55 (24.8)	43 (20.9)	0.77 (0.43–1.38)	0.69 (0.45–1.07)
3Q	25 (24.8)	125 (32.0)	0.49 (0.26–0.93)	56 (25.2)	43 (20.9)	0.80 (0.45–1.43)	0.64 (0.40–1.03)
4Q	25 (24.8)	108 (27.6)	0.50 (0.26–0.99)	55 (24.8)	86 (41.8)	0.39 (0.23–0.67)	0.43 (0.28–0.65)
	P for trend		**0.043**			**0.001**	
Lignan							
Enterolactone[g]							
1Q	26 (25.7)	105 (26.9)	1.00 (ref)	74 (33.3)	73 (35.4)	1.00 (ref)	1.00 (ref)
2Q	26 (25.7)	92 (23.5)	1.09 (0.58–2.05)	37 (16.7)	25 (12.1)	1.47 (0.80–2.69)	1.27 (0.82–1.97)
3Q	24 (23.8)	79 (20.2)	1.14 (0.60–2.17)	56 (25.2)	53 (25.7)	1.04 (0.63–1.70)	1.08 (0.73–1.59)
4Q	25 (24.8)	115 (29.4)	0.83 (0.44–1.56)	55 (24.8)	55 (26.7)	0.99 (0.60–1.62)	0.93 (0.63–1.37)
	P for trend		0.588			0.849	

Bold values indicate *P*-value less than 0.05.
[a] Adjusted for age, sex, resident area, smoking, alcohol consumption, body mass index, education level, vegetable intake and fruit intake.
[b] Adjusted for age, sex, and resident area.
[c] *P* for heterogeneity >0.05.
[d] Cut-offs for quartiles were 87, 163, 404 ng/ml in Korean study, and 90, 190.5, 506 ng/ml in Vietnamese study.
[e] Cut-offs for quartiles were 26.4, 68.0, 134.1 ng/ml in Korean study, and 7.6, 32.6, 65.9 ng/ml in Vietnamese study.
[f] Total isoflavone was considered as sum of genistein and daidzein level. Cut-offs for quartiles were 130, 225, 540 ng/ml in Korean study, and 103, 220, 563 ng/ml in Vietnamese study.
[g] Cut-offs for quartiles were 29, 65.7, 118 ng/ml in Korean study, and 0, 2.25, 10.5 ng/ml in Vietnamese study.

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CI = 0.28–0.82 for daidzein; and OR = 0.39, 95% CI = 0.23–0.67 for total isoflavone). The highest quartile of genistein, daidzein, and total isoflavone had inverse association with colorectal cancer in the meta-analysis and there is no heterogeneity in the colorectal cancer risk in relation to plasma isoflavone concentrations between Koreans and Vietnamese (P for heterogeneity of Q test > 0.05).

Although enterolactone concentration was so different between Korean and Vietnamese population, plasma enterolactone levels had no significant association with colorectal cancer both in Korean and Vietnamese.

3.3. Colorectal cancer risk and phytoestrogens concentrations according to sex

When the study population was stratified by sex, the beneficial association of isoflavone with colorectal cancer risk was observed both in women and men (Table 3). In Korean women, there was a dose-response relationship, with marginal significance, in the concentrations of genistein and total isoflavone in relation to the colorectal cancer risk (P for trend = 0.092 for genistein and 0.051 for total isoflavone, respectively). In Vietnamese women, the highest concentration categories of genistein, daidzein, and total isoflavone were associated with a decreased risk of colorectal cancer (OR = 0.38, 95% CI = 0.19–0.76 for genistein; OR = 0.41, 95% CI = 0.19–0.86 for daidzein; and OR = 0.38, 95% CI = 0.18–0.79 for total isoflavone), and a significant dose-response relationship was observed. The highest quartile of genistein, daidzein, and total isoflavone were inversely associated with colorectal cancer in the meta-analysis (COR = 0.43, 95% CI = 0.25–0.76 for genistein; COR = 0.50, 95% CI = 0.28–0.88 for daidzein; and COR = 0.43, 95% CI = 0.24–0.77 for total isoflavone). Although the concentrations of isoflavones were not significantly associated with the colorectal cancer risk in Korean and Vietnamese men, the highest quartile of genistein and total isoflavone had significant relationship with colorectal cancer in meta-analysis (COR = 0.48, 95% CI = 0.26–0.90 for genistein; and COR = 0.47, 95% CI = 0.25–0.88 for total isoflavone). However, plasma enterolactone levels were not associated with colorectal cancer in men and women.

3.4. Colorectal cancer risk and plasma concentrations of phytoestrogens according to colon and rectum cancer

When cases were stratified by colon and rectal cancer, the beneficial association of isoflavone was shown both in colon cancer and rectal cancer (Table 4). In the meta-analysis, the highest quartile of genistein, daidzein, and total isoflavone were inversely associated with colon cancer risk (COR = 0.41, 95% CI = 0.22–0.75 for genistein; COR = 0.43, 95% CI = 0.26–0.73 for daidzein; and COR = 0.44, 95% CI = 0.25–0.78 for total isoflavone). The highest quartile of genistein and total isoflavone were inversely associated with rectal cancer (COR = 0.55, 95% CI = 0.32–0.92 for genistein; and COR = 0.54, 95% CI = 0.32–0.91 for total isoflavone). Plasma enterolactone concentrations were not associated with colorectal cancer risk in Korean and Vietnamese regardless of sex and anatomical subtype.

4. Discussion

In the nested case-control study of a prospective study in Korea, the isoflavones biomarker, which reflects soybean product intake, had association with a decreased colorectal cancer risk. This result in Korean samples was replicated in a case-control study with a Vietnamese sample. Although the median level of isoflavone concentration was different in the Korean and Vietnamese samples, the odds ratios of the significant association between isoflavone and colorectal cancer were similar within the each categories.

The relationship between soybean consumption and colorectal cancer risk is biologically plausible, as the association can be explained by several mechanisms in animal models. Isoflavone can inhibit the proliferation of colon cancer cells and enhance apoptosis by interacting with several pathways [15]. The increased expression of fatty acid synthases induces tumorigenesis earlier, but soy protein can inhibit DNA damage by decreasing the expression of colon fatty acid synthase [16]. Dietary protein from soybean products is related with reductions of polyamine production in intestinal mucosa [17] and the induction of somatostatin, which is an anti-proliferative agent for colon cancer cells [18]. Soy protein also displays a protective effect on colon cancer risk by increasing fecal fat excretion [19].

However, human epidemiologic studies about the relationship between soybean consumption and colorectal cancer risk are limited. In a cohort study among Chinese women, each increased 5 g per day of soybean products consumption was related with an 8% decrease of colorectal cancer risk, and women who consumed more than 21 g/day of soy foods were related with a 33% lower risk of colorectal cancer compared with women who consumed less than 12.8 g/day [7]. However, in a US cohort study among women, tofu intake had no association with colorectal cancer incidence [20]. In a Japanese cohort study, soy food consumption was not associated with colorectal cancer in men or women [8]. In another Japanese cohort study, high intake of soy products had relationship with a 44% decreased risk of colon cancer in women, but no association was observed between the intake of soy products and colon cancer in men [9]. In a large case-control study conducted in Korea, the association of isoflavone intake was associated with overall colorectal cancer and this association was more relevant in post-menopause women and in distal colon [21]. Our results were concordant with recent two meta-analyses which reported that soybean product intake was associated with colorectal cancer, especially, in Asian population and in case-control studies [22,23].

Obvious evidences in relation to anti-carcinogenic ability of isoflavone for colorectal cancer have been clarified by animal and in vitro studies [15–19], but reports from prior epidemiology studies have been not consistent [7–10,20,21], and these inconsistencies should be evaluated. First, error in the measurement of soybean consumption can make a result toward to null. In the most of prior studies, FFQ was used to quantify soybean or isoflavone consumption. Because FFQ depends on memory, FFQ is typically more sensitive to information bias or measurement error than biomarker measurements [11,12]. Second, geographical variation in levels of soybean consumption may produce inconsistent results. Energy-adjusted isoflavone consumption per day is various according to race and ethnicity [5,24,25]. In a nested case-control study conducted in Europe, isoflavone biomarkers in serum were used to assess the colorectal cancer risk, and there was no association with colorectal cancer in spite of a large sample size [25]. Median of isoflavone blood concentrations in our populations were more than 30 times that in Western populations [25]. In a nested case-control study in Europe, the median levels of genistein and daidzein were 6.25 ng/ml and 2.20 ng/ml, respectively [25], but in our nested case-control study in Korea, the median levels of genistein and daidzein were 205 ng/ml and 69.9 ng/ml, respectively. Isoflavone concentration in the highest quartile group in Western populations was lower than that in even the lowest quartile group in our study populations. In Western populations, the association of soybean products with colorectal cancer may be underestimated or masked due to low levels of soybean product intake. Prospective studies using biomarkers in Asian populations

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Table 3
Colorectal cancer risk and plasma concentrations of phytoestrogens in Korean and Vietnamese, stratified by sex.

Phytoestrogen (ng/mL)	Korean			Vietnamese			Meta-analysis COR (95% CI)[c]
	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[b]	
	No. (%)	No. (%)		No. (%)	No. (%)		
Women	*N* = 53	*N* = 206		*N* = 117	*N* = 114		
Genistein[d]							
1Q	14 (26.4)	29 (14.1)	1.00 (ref)	30 (25.6)	20 (17.5)	1.00 (ref)	1.00 (ref)
2Q	13 (24.5)	43 (20.9)	0.63 (0.25–1.58)	29 (24.8)	19 (16.7)	0.99 (0.44–2.23)	0.81 (0.44–1.49)
3Q	13 (24.5)	84 (40.8)	0.33 (0.14–0.81)	29 (24.8)	24 (21.1)	0.83 (0.38–1.81)	0.54 (0.22–1.32)
4Q	13 (24.5)	50 (24.3)	0.54 (0.22–1.36)	29 (24.8)	51 (44.7)	0.38 (0.19–0.79)	0.43 (0.25–0.76)
	P for trend		0.092			**0.005**	
Daidzein[e]							
1Q	14 (26.4)	45 (21.8)	1.00 (ref)	30 (25.6)	18 (15.8)	1.00 (ref)	1.00 (ref)
2Q	13 (24.5)	49 (23.8)	0.77 (0.32–1.90)	29 (24.8)	27 (23.7)	0.63 (0.29–1.39)	0.69 (0.38–1.24)
3Q	13 (24.5)	51 (24.8)	0.76 (0.31–1.87)	29 (24.8)	26 (22.8)	0.66 (0.30–1.45)	0.70 (0.39–1.27)
4Q	13 (24.5)	61 (29.6)	0.65 (0.27–1.56)	29 (24.8)	43 (37.7)	0.41 (0.19–0.86)	0.50 (0.28–0.88)
	P for trend		0.352			**0.025**	
Total isoflavone[f]							
1Q	14 (26.4)	30 (14.6)	1.00 (ref)	30 (25.6)	20 (17.5)	1.00 (ref)	1.00 (ref)
2Q	13 (24.5)	36 (17.5)	0.68 (0.27–1.74)	29 (24.8)	22 (19.3)	0.85 (0.38–1.89)	0.77 (0.42–1.42)
3Q	13 (24.5)	90 (43.7)	0.28 (0.12–0.70)	29 (24.8)	21 (18.4)	0.94 (0.42–2.09)	0.52 (0.16–1.71)[l]
4Q	13 (24.5)	50 (24.3)	0.52 (0.21–1.33)	29 (24.8)	51 (44.7)	0.38 (0.18–0.79)	0.43 (0.24–0.77)
	P for trend		0.051			**0.008**	
Enterolactone[g]							
1Q	14 (26.4)	52 (25.2)	1.00 (ref)	36 (30.8)	40 (35.1)	1.00 (ref)	1.00 (ref)
2Q	13 (24.5)	41 (19.9)	1.21 (0.50–2.96)	23 (19.7)	16 (14.0)	1.53 (0.70–3.37)	1.38 (0.77–2.49)
3Q	13 (24.5)	46 (22.3)	0.99 (0.41–2.40)	29 (24.8)	26 (22.8)	1.22 (0.61–2.46)	1.13 (0.65–1.95)
4Q	13 (24.5)	67 (32.5)	0.70 (0.30–1.66)	29 (24.8)	32 (28.1)	1.00 (0.51–1.97)	0.87 (0.51–1.48)
	P for trend		0.359			0.986	
Men	*N* = 48	*N* = 185		*N* = 105	*N* = 92		
Genistein[h]							
1Q	12 (25.0)	36 (19.5)	1.00 (ref)	27 (25.7)	16 (17.4)	1.00 (ref)	1.00 (ref)
2Q	12 (25.0)	51 (27.6)	0.59 (0.23–1.54)	26 (24.8)	26 (28.3)	0.59 (0.26–1.35)	0.59 (0.32–1.10)
3Q	12 (25.0)	38 (20.5)	0.86 (0.33–2.27)	26 (24.8)	18 (19.6)	0.85 (0.36–2.02)	0.85 (0.45–1.63)
4Q	12 (25.0)	60 (32.4)	0.49 (0.18–1.30)	26 (24.8)	32 (34.8)	0.48 (0.22–1.08)	0.48 (0.26–0.90)
	P for trend		0.270			0.150	
Daidzein[i]							
1Q	12 (25.0)	39 (21.1)	1.00 (ref)	27 (25.7)	18 (19.6)	1.00 (ref)	1.00 (ref)
2Q	12 (25.0)	55 (29.7)	0.71 (0.28–1.79)	26 (24.8)	19 (20.7)	0.92 (0.40–2.13)	0.82 (0.44–1.52)
3Q	12 (25.0)	40 (21.6)	1.03 (0.39–2.71)	26 (24.8)	21 (22.8)	0.82 (0.36–1.89)	0.90 (0.48–1.70)
4Q	12 (25.0)	51 (27.6)	0.74 (0.29–1.90)	26 (24.8)	34 (37.0)	0.51 (0.23–1.12)	0.60 (0.33–1.09)
	P for trend		0.722			0.080	
Total isoflavone[j]							
1Q	12 (25.0)	36 (19.5)	1.00 (ref)	27 (25.7)	14 (15.2)	1.00 (ref)	1.00 (ref)
2Q	12 (25.0)	53 (28.7)	0.65 (0.25–1.68)	26 (24.8)	25 (27.2)	0.54 (0.23–1.25)	0.59 (0.31–1.10)
3Q	12 (25.0)	35 (18.9)	0.98 (0.37–2.56)	26 (24.8)	21 (22.8)	0.64 (0.27–1.52)	0.77 (0.41–1.47)
4Q	12 (25.0)	61 (33.0)	0.54 (0.20–1.41)	26 (24.8)	32 (34.8)	0.42 (0.18–0.96)	0.47 (0.25–0.88)
	P for trend		0.349			0.073	
Enterolactone[k]							
1Q	12 (25.0)	55 (29.7)	1.00 (ref)	38 (36.2)	33 (35.9)	1.00 (ref)	1.00 (ref)
2Q	12 (25.0)	43 (23.2)	1.24 (0.49–3.14)	15 (14.3)	10 (10.9)	1.30 (0.52–3.29)	1.27 (0.66–2.44)
3Q	12 (25.0)	42 (22.7)	1.26 (0.50–3.18)	26 (24.8)	29 (31.5)	0.78 (0.39–1.59)	0.93 (0.53–1.63)
4Q	12 (25.0)	45 (24.3)	1.29 (0.51–3.27)	26 (24.8)	20 (21.7)	1.13 (0.53–2.38)	1.19 (0.66–2.14)
	P for trend		0.603			0.947	

Bold values indicate *P*-value less than 0.05.
[a] Adjusted for age, resident area, smoking, alcohol consumption, body mass index, education level, vegetable intake and fruit intake.
[b] Adjusted for age and resident area.
[c] *P* for heterogeneity >0.05 except for (l).
[d] Cut-offs for quartiles were 81, 154, 459 ng/ml in Korean study, and 88, 191, 435 ng/ml in Vietnamese study.
[e] Cut-offs for quartiles were 28, 62, 134 ng/ml in Korean study, and 6.2, 32.9, 66 ng/ml in Vietnamese study.
[f] Total isoflavone was considered as sum of genistein and daidzein level. Cut-offs for quartiles were 129, 212, 610 ng/ml in Korean study, and 103, 230, 515 ng/ml in Vietnamese study.
[g] Cut-offs for quartiles were 30, 65.7, 121 ng/ml in Korean study, and 0, 2.5, 10.0 ng/ml in Vietnamese study.
[h] Cut-offs for quartiles were 90, 186, 362 ng/ml in Korean study, and 92, 219, 620 ng/ml in Vietnamese study.
[i] Cut-offs for quartiles were 25, 74, 152 ng/ml in Korean study, and 8.3, 32, 63 ng/ml in Vietnamese study.
[j] Total isoflavone was considered as sum of genistein and daidzein level. Cut-offs for quartiles were 134, 281, 489 ng/ml in Korean study, and 105, 240, 693 ng/ml in Vietnamese study.
[k] Cut-offs for quartiles were 30, 58, 116 ng/ml in Korean study, and 0, 2.3, 13 ng/ml in Vietnamese study.

are crucial to assess the association of soybean products with colorectal cancer. Third, the discrepancy of epidemiologic studies might be caused from different equol producing rate between ethnicity. There are evidences that clinical efficacy of isoflavone is dependent on equol that is transformed from daidzein by gut bacteria [26]. Although 60–80% of Asians can make equol in the gut after eating soybean foods, only 30–40% of Western populations can make equol [27,28].

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Table 4
Colorectal cancer risk and plasma phytoestrogens concentrations, stratified by colon and rectum cancers.

Phytoestrogen (ng/mL)	Korean (Discovery phase)			Vietnamese (Replication phase)			Meta-analysis COR (95% CI)[c]
	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[b]	
	No. (%)	No. (%)		No. (%)	No. (%)		
Colon	*N* = 60	*N* = 391		*N* = 102	*N* = 206		
Genistein[d]							
1Q	15 (25.0)	64 (16.4)	1.00 (ref)	26 (25.5)	29 (14.1)	1.00 (ref)	1.00 (ref)
2Q	15 (25.0)	66 (16.9)	0.88 (0.39–2.00)	25 (24.5)	38 (18.5)	0.74 (0.35–1.54)	0.80 (0.46–1.39)
3Q	15 (25.0)	164 (41.9)	0.36 (0.16–0.79)	26 (25.5)	50 (24.3)	0.57 (0.28–1.17)	0.47 (0.27–0.79)
4Q	15 (25.0)	97 (24.8)	0.58 (0.26–1.32)	25 (24.5)	89 (43.2)	0.31 (0.16–0.62)	0.41 (0.22–0.75)
	P for trend		0.050			**0.001**	
Daidzein[e]							
1Q	15 (25.0)	66 (16.9)	1.00 (ref)	26 (25.5)	32 (15.5)	1.00 (ref)	1.00 (ref)
2Q	15 (25.0)	109 (27.9)	0.52 (0.23–1.17)	25 (24.5)	42 (20.4)	0.73 (0.36–1.51)	0.63 (0.37–1.08)
3Q	15 (25.0)	102 (26.1)	0.62 (0.27–1.40)	26 (25.5)	51 (24.8)	0.63 (0.31–1.27)	0.63 (0.37–1.07)
4Q	15 (25.0)	114 (29.2)	0.52 (0.23–1.18)	25 (24.5)	81 (39.3)	0.38 (0.19–0.75)	0.43 (0.26–0.73)
	P for trend		0.224			**0.004**	
Total isoflavone[f]							
1Q	15 (25.0)	60 (15.4)	1.00 (ref)	26 (25.5)	31 (15.1)	1.00 (ref)	1.00 (ref)
2Q	15 (25.0)	76 (19.4)	0.76 (0.34–1.74)	25 (24.5)	32 (15.5)	0.95 (0.45–2.00)	0.86 (0.50–1.49)
3Q	15 (25.0)	165 (42.2)	0.34 (0.15–0.76)	26 (25.5)	54 (26.2)	0.57 (0.28–1.15)	0.46 (0.27–0.78)
4Q	15 (25.0)	90 (23.0)	0.62 (0.27–1.43)	25 (24.5)	89 (43.2)	0.34 (0.17–0.67)	0.44 (0.25–0.78)
	P for trend		0.084			**<0.001**	
Enterolactone[g]							
1Q	15 (25.0)	115 (29.4)	1.00 (ref)	45 (44.1)	73 (35.4)	1.00 (ref)	1.00 (ref)
2Q	15 (25.0)	78 (20.0)	1.39 (0.63–3.07)	6 (5.9)	8 (3.9)	1.27 (0.41–3.93)	1.35 (0.71–2.58)
3Q	15 (25.0)	69 (17.7)	1.71 (0.77–3.78)	26 (25.5)	47 (22.8)	0.91 (0.50–1.67)	1.18 (0.64–2.17)
4Q	15 (25.0)	129 (33.0)	0.85 (0.39–1.84)	25 (24.5)	78 (37.9)	0.53 (0.29–0.94)	0.63 (0.39–1.01)
	P for trend		0.737			**0.041**	
Rectum	*N* = 41	*N* = 391		*N* = 120	*N* = 206		
Genistein[h]							
1Q	11 (26.8)	82 (21.0)	1.00 (ref)	30 (25.0)	39 (18.9)	1.00 (ref)	1.00 (ref)
2Q	11 (26.8)	138 (35.3)	0.57 (0.23–1.40)	30 (25.0)	46 (22.3)	0.85 (0.44–1.66)	0.74 (0.43–1.26)
3Q	9 (22.0)	57 (14.6)	1.10 (0.42–2.87)	30 (25.0)	43 (20.9)	0.94 (0.48–1.83)	0.99 (0.57–1.71)
4Q	10 (24.4)	114 (29.2)	0.63 (0.25–1.61)	30 (25.0)	78 (37.9)	0.51 (0.27–0.97)	0.55 (0.32–0.92)
	P for trend		0.645			**0.046**	
Daidzein[i]							
1Q	11 (26.8)	135 (34.5)	1.00 (ref)	30 (25.0)	42 (20.4)	1.00 (ref)	1.00 (ref)
2Q	10 (24.4)	88 (22.5)	1.42 (0.57–3.55)	30 (25.0)	43 (20.9)	1.02 (0.52–1.98)	1.15 (0.67–1.96)
3Q	11 (26.8)	45 (11.5)	3.26 (1.29–8.23)	30 (25.0)	45 (21.8)	0.94 (0.48–1.81)	1.68 (0.50–5.65)[l]
4Q	9 (22.0)	123 (31.5)	0.91 (0.36–2.31)	30 (25.0)	76 (36.9)	0.57 (0.30–1.07)	0.66 (0.39–1.12)
	P for trend		0.799			0.064	
Total isoflavone[j]							
1Q	11 (26.8)	88 (22.5)	1.00 (ref)	30 (25.0)	38 (18.5)	1.00 (ref)	1.00 (ref)
2Q	10 (24.4)	107 (27.4)	0.78 (0.31–1.95)	30 (25.0)	47 (22.8)	0.82 (0.42–1.60)	0.81 (0.47–1.38)
3Q	10 (24.4)	70 (17.9)	1.13 (0.45–2.86)	30 (25.0)	41 (19.9)	0.96 (0.49–1.89)	1.02 (0.59–1.75)
4Q	10 (24.4)	126 (32.2)	0.65 (0.26–1.63)	30 (25.0)	80 (38.8)	0.49 (0.26–0.93)	0.54 (0.32–0.91)
	P for trend		0.494			**0.036**	
Enterolactone[k]							
1Q	11 (26.8)	103 (26.3)	1.00 (ref)	30 (25.0)	76 (36.9)	1.00 (ref)	1.00 (ref)
2Q	10 (24.4)	96 (24.6)	0.97 (0.38–2.45)	30 (25.0)	30 (14.6)	2.48 (1.28–4.81)	1.65 (0.66–4.10)
3Q	10 (24.4)	89 (22.8)	0.98 (0.39–2.46)	30 (25.0)	61 (29.6)	1.25 (0.68–2.29)	1.16 (0.70–1.93)
4Q	10 (24.4)	103 (26.3)	0.92 (0.36–2.33)	30 (25.0)	39 (18.9)	1.98 (1.05–3.76)	1.46 (0.70–3.05)
	P for trend		0.870			0.125	

Bold values indicate *P*-value less than 0.05.
[a] Adjusted for age, resident area, smoking, alcohol consumption, body mass index, education level, vegetable intake and fruit intake.
[b] Adjusted for age and resident area.
[c] *P* for heterogeneity >0.05 except for (l).
[d] Cut-offs for quartiles were 85, 142, 430 ng/ml in Korean study, and 76, 166, 430.5 ng/ml in Vietnamese study.
[e] Cut-offs for quartiles were 23, 62, 136 ng/ml in Korean study, and 4.7, 28.3, 61 ng/ml in Vietnamese study.
[f] Total isoflavone was considered as sum of genistein and daidzein level. Cut-offs for quartiles were 124, 214, 640 ng/ml in Korean study, and 94.3, 190, 494 ng/ml in Vietnamese study.
[g] Cut-offs for quartiles were 32.5, 65, 105 ng/ml in Korean study, and 0, 0.7, 6.25 ng/ml in Vietnamese study.
[h] Cut-offs for quartiles were 102, 239, 389 ng/ml in Korean study, and 97, 221, 590 ng/ml in Vietnamese study.
[i] Cut-offs for quartiles were 45, 85, 128 ng/ml in Korean study, and 11, 34.1, 66 ng/ml in Vietnamese study.
[j] Total isoflavone was considered as sum of genistein and daidzein level. Cut-offs for quartiles were 151, 304, 491 ng/ml in Korean study, and 115, 270, 656 ng/ml in Vietnamese study.
[k] Cut-offs for quartiles were 28, 67, 131 ng/ml in Korean study, and 0.21, 3.6, 19.7 ng/ml in Vietnamese study.

In our Korean and Vietnamese study, the beneficial association of isoflavone with colorectal cancer was observed in women but not in men, although combined odds ratios in meta-analysis were significant both in men and women. We hypothesized that sex hormones in women may prevent from colorectal cancer by binding to estrogen receptors in the intestinal mucosa [29]. Previous studies in relation to the association between gender and colorectal cancer mortality reported lower mortality for women, especially premenopausal women and women who used hormone therapy [3,30]. In a Japanese case-control study, hormonal

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reproductive factors such as age at menarche, age at first pregnancy and age at first full-term pregnancy had a strong association with the colorectal cancer risk, especially distal colon cancer [31]. The Women's Health Initiative study found that hormone replacement therapy was associated with reduced risk of colon cancer by 30% and rectal cancer by 43% [32]. Our results are consistent with a meta-analysis that suggested that the intake of soybean products was associated with a decrease in colorectal cancer risk for women [33].

The strengths of our study is that measurement of isoflavone levels in blood provides an intake index and assesses the metabolic process of isoflavones; thus, blood concentrations can more accurately reveal appropriate biological dose levels. As indirect measures of dietary isoflavone or soybean product intake, FFQs are limited in their ability to measure individual variability; therefore, the true association between colorectal cancer and soybean products may be diluted when FFQs are used. Second, our design of Korean study was nested case-control study and so using prediagnosis plasma reduces the potential recall bias for exposure among colorectal cancer cases. Also cases and their matched controls were selected from the same populations, so we can avoid the selection bias.

However, we should note our limitations in relation to assessing the causal association of isoflavone levels with the colorectal cancer risk. First, we quantified the plasma phytoestrogen level once at the time of recruitment and half-life of phytoestrogen in the body is short [34]. We assumed that soybean product intake in our study populations are stable for a long time like Japanese population [35,36]. We collected samples in the early morning before first meal of the day to reduce the measurement error due to time. Misclassification caused from plasma measurement would be non-differential and this misclassification would under-estimate the associations. Second, the sample size in the present study was small, and we were unable to conduct subtype analyses according to sub-sites of proximal and distal colon cancer due to insufficient statistical power. Because etiological hormonal factors may more affect the risk of distal rather than proximal colon cancer and the incidence of distal colon cancer is rapidly increasing in Korea, isoflavone may produce different effects on proximal and distal colon cancers [31,37]. Also we were unable to conduct subtype analyses according to menopausal status and use of hormone replacement therapy because of small sample size, although menopausal status and use of hormone replacement therapy could be an important effect modifier [21,38]. Third, a soybeans consumption may have correlation with healthy diet habit. Although we adjusted for correlated variables such as the vegetables and fruits intake in Korean population, we might remain potential confounders including other healthy foods. Forth, because our study population of Korean nested case-control study was recruited voluntarily in community and that of Vietnamese case-control study was selected from hospital patients, our results could not guarantee external validity.

In conclusion, this study suggests that isoflavone may have a role in lowering the colorectal cancer risk, especially in women, regardless of different ethnic background. Further evaluation with larger studies across various ethnic groups is needed in elucidating the relationship between isoflavone and colorectal cancer.

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Statement of authorship

KPK, YY, and SKP designed the research; KPK, JHY, CSK, YKL, and CHK conducted research; ST, LTN, CK, SHC, HRS, DK, SKP, and KYY collected data; KPK and YY analyzes data; KPK wrote the manuscript and KYY had primary responsibility for the final contents. All authors read, checked and approved.

Conflict of interest

All authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2017.07.014

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