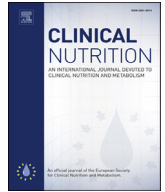




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Original article

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, enterolactone 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.

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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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