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Legume consumption and incident sporadic colorectal adenoma risk: A pooled case-control study

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Legume consumption and incident sporadic colorectal adenoma risk: A pooled case-control study

By

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Bachelor of Medicine
Central South University
2013

Thesis Committee Chair: Roberd M. Bostick, MD, MPH

An abstract of
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Abstract

Legume consumption and incident sporadic colorectal adenoma risk: A pooled case-control study

By Sijia Ma

Purpose: Legumes, especially soy, have multiple potential anti-colon carcinogenic properties. Several studies investigated associations of legumes and soy with colorectal cancer risk, but the results across the studies are inconsistent and few of the studies were conducted in a United States populations.

Methods: We conducted a pooled analysis of data from three colonoscopy-based case-control studies of incident, sporadic colorectal adenoma (pooled n=794 cases and 994 controls) conducted in Minnesota, North Carolina, and South Carolina between 1991 and 2002. Dietary intakes were assessed using semi-quantitative food frequency questionnaires.

Results: The multivariable-adjusted odds ratios (OR) with 95% confidence intervals (CI) for those in the second and third tertiles of total legume consumption relative to those in the lowest were, respectively, 1.18 (CI 0.91 – 1.51) and 1.12 (CI 0.82 – 1.53), and for soy consumption, 1.13 (0.88 – 1.47) and 0.96 (0.71 – 1.28). The ORs and 95% CIs for those above relative to those below the sex-specific median intakes of total legumes and soy in the controls were, respectively, 0.54 (CI 0.24 – 1.19) and 0.96 (CI 0.46 – 2.03) among premenopausal women and 0.89 (CI 0.54 – 1.47) and 0.68 (CI 0.41 – 1.11) among postmenopausal women who took exogenous estrogens.

Conclusion: Our findings provide no support for associations of total legume intake or soy foods intakes overall with risk for incident, sporadic colorectal adenoma, but do suggest the possibility that legume or soy intake may be inversely associated with adenomas among women with a positive estrogen status (i.e. premenopausal or taking exogenous estrogens).

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Background

Descriptive epidemiology of colorectal cancer

Colorectal cancer (CRC) is the third most common cancer diagnosed and the second leading cause of cancer deaths among men and women combined in the United States. In 2014, it is expected that 136,830 people will be diagnosed with CRC, and 50,310 individuals will die from the disease (American Cancer Society 2014). During the past 20 years, the incidence rate has decreased significantly, most likely due to the improved and more compliantly followed screening practices. Mortality rates also have decreased by almost 25%, resulting mostly from enhanced treatment and earlier detection. Incidence and death rates for colorectal cancer increase with age. Approximately 90% of new cases and deaths occur in people 50 and older (Society AC. Colorectal Cancer facts & figures 2014 - 2016).

International studies have observed that the incidence of CRC varies substantially across countries. The age-standardized incidence rate of CRC in Asian countries (e.g., China and Japan) is lower than that in North America and European countries, and the incidence increases substantially in migrants from low-risk to high-risk areas. In contrast to the trend in the US, CRC incidence worldwide increased significantly in Eastern European countries, Asian countries, and some South American countries . Incidence increases substantially in migrants from low-risk to high-risk areas. For example, Japanese, Chinese, and Koreans who migrated to the United States had a higher incidence rate of CRC than their counterparts in their home countries. Their descendants tended to acquire the incidence rates in the United States (Flood, Weiss *et al.* 2000).

Polyps and Molecular Pathogenesis

Most CRC arise from adenomatous polyps, and it is believed that they share a common etiopathogenesis (Tantamango, Knutsen *et al.* 2011). A polyp may be classified pathologically as a nonneoplastic hamartoma (juvenile polyp), a hyperplastic mucosal proliferation (hyperplastic polyp), or an adenomatous polyp. Only adenomas are clearly premalignant and the likelihood of transforming into a cancer depends on the gross appearance of the lesion, its histologic features, and its size. Adenomatous polyps may be pedunculated (stalked) or sessile (flat-based). Cancers are more likely to develop in sessile polyps. Histologically, adenomatous polyps may be tubular, villous (i.e., papillary), or tubulovillous. Villous adenomas, most of which are sessile, become malignant more than three times as often as tubular adenomas. The likelihood that any polypoid lesion in the large bowel contains invasive cancer is related to the size of the polyp, being negligible (<2%) in lesions < 1.5 cm, intermediate (2-10%) in lesions 1.5 - 2.5 cm, and substantial (10%) in lesions >2.5 cm in size (Glovannucci, Wu.2006). Large polyps are more likely to progress to invasive cancer than are small ones.

Several molecular changes are noted in adenomatous polyps, dysplastic lesions, and polyps containing microscopic foci of tumor cells (carcinoma-in-situ), which are thought to reflect a multistep process in the evolution of normal colonic mucosa to life-threatening invasive carcinoma. These developmental steps toward carcinogenesis include, but are not restricted to, loss of DNA (allelic loss) at the site of a tumor-suppressor gene [the adenomatous polyposis coli (*APC*) gene] on the long arm of chromosome 5 (5q21); point mutations in the *K-ras* protooncogene; hypomethylation of DNA, leading to gene activation; allelic loss at the site of a tumor-suppressor gene located on chromosome 18q; and allelic

loss at chromosome 17p, associated with mutations in the *p53* tumor suppressor gene. Thus, the altered proliferative pattern of the colonic mucosa, which results in progression to a polyp and then to carcinoma, may involve the mutational activation of an oncogene followed by and coupled with the loss of genes that normally suppress tumorigenesis. It remains uncertain whether the genetic aberrations always occur in a defined order. Based on this model, however, cancer is believed to develop only in those polyps in which most (if not all) of these mutational events take place (Glovannucci, Wu.2006).

Analytical epidemiology of colorectal cancer

The risk of getting CRC increases as people age. More than 90% of cases occur in people who are 50 years old or older. Men have a higher incidence rate than women. Other risk factors include having inflammatory bowel disease, including Crohn's disease or ulcerative colitis; a personal or family history of colorectal cancer or colorectal polyps; and a genetic syndrome such as familial adenomatous polyposis (FAP) or hereditary non-polyposis CRC (Lynch syndrome). Lifestyle factors that may contribute to a higher risk of CRC include lack of regular physical activity, low fruit and vegetable intake, a low-fiber and high-fat diet, overweight and obesity, alcohol consumption, and tobacco use.

A recent study of dietary exposures and their impact on colorectal cancer risk concluded that there is convincing evidence that red and processed meat intake and higher alcohol consumption are associated with higher risk of colorectal cancer among men, while dietary fiber, garlic, milk, calcium, fruits, non-starchy vegetables, and vitamin D are associated with lower colorectal cancer risk. However, no conclusive conclusion can be made about associations of colorectal cancer with fish, glycemic index, folate, dietary patterns, vitamin C,

vitamin E, and selenium. (Baena and Salinas 2015). Physical activity is consistently associated with lower risk of CRC; recent studies found that those subjects who are more physically active have a 24% lower risk of CRC compared to those with more sedentary lifestyles (Wolin, Yan *et al.* 2009). Obesity, defined as a body mass index (BMI, kg/m^2) greater than 30 kg/m^2, and overweight, defined as a BMI between 25 and 29.9 kg/m^2, are associated with higher risk of CRC (Perera *et al.* 2012). Subjects with a BMI greater than 30 have a 19% higher risk of CRC compared to those with a BMI between 20 and 25 (Tarraga *et al.* 2013). Observational epidemiologic studies and randomized colorectal adenoma recurrence trials strongly support that long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) reduces risk for CRC (Stolfi, De Simone *et al.* 2013). Data from multiple prospective and retrospective cohorts indicate that hormone replacement therapy (HRT) in postmenopausal women is inversely associated with incidence of colorectal cancer. A Women's Health Initiative clinical trial found a statistically significant 56% lower risk of colon cancer with the use of HRT in postmenopausal women (Barzi, Lenz *et al.* 2013).

Legumes

Legumes are a diverse group of foods that include soybeans, peas, beans, chickpeas lentils, peanuts, and other podded plants. They are rich in protein and are important sources of dietary fiber, resistant starch, folate, selenium, saponins, protease inhibitors, lectins, phytates, and isoflavones with potential anticancer effects. Legumes, regarded as "poor man's meat", have played a significant role in the traditional diets of Asia, South America, and the Middle East for thousands of years, while in western countries, such as America and Europe, their consumption is more limited (Messina 1999).

Several epidemiologic studies found that a high intake of legumes was associated with a lower risk of CRC, but the results across the studies are inconsistent. A most recent meta-analysis of 14 cohort studies with 1,903,459 participants and 12,261 cases found that a higher intake of legumes was statistically significantly associated with a 10% lower risk of colorectal cancer, but not within the United States population (Zhu, Sun *et al.* 2015). Another meta-analysis of 3 cohort and 11 case-control studies with a total of 101,856 subjects and 8,380 cases found that a higher intake of legumes was statistically significantly associated with lower risk of colorectal adenoma, including a statistically significant 12% lower risk in populations in the United States (Wang, Wang *et al.* 2013). In another meta-analysis, which included 4 cohort and 7 case-control studies, of soy intake and colorectal cancer found a 21% lower colorectal cancer risk among women who consumed higher soy foods, but not in men. No statistically significant association, overall or stratified by sex, was found in Western counties. (Yan, Spitznagel *et al.* 2010). Michels et al. found that women who consumed four or more servings of legumes per week had a 33% lower incidence of colorectal adenomas than did women who consumed one serving per week or less. (Michels, Giovannucci *et al.* 2006).

Animal studies fairly consistently found that a soy diet or isoflavones inhibited the formation of aberrant crypt foci, a well accepted precursor of CRC and CRA, but no clear conclusions regarding the development of chemically-induced CRC (Toyomura and Kono 2002). A clinical study observed that higher consumption of vegetables (including legumes) led to down-regulation of genes that promote cell proliferation and bioactivation of procarcinogens and up-regulation of genes involved in cell growth arrest in normal intestinal mucosa from both adenoma patients and healthy controls. In addition, the authors found

that genes modulated by vegetable intake were responsible for comparatively later stages of the development of colorectal neoplasms in patients with CRA, while genes modulated in healthy controls were involved in the initial stage, which indicated that possible protective effects of legumes may be most apparent in the earlier states of colorectal carcinogenesis (van Breda, van Agen *et al.* 2004). However, among the limited clinical studies, one small scale randomized intervention clinical trial found that supplementation with soy protein containing isoflavones did not reduce colorectal epithelial cell proliferation in men and women (Adams, Lampe *et al.* 2005).

Given that a great variety of anti-carcinogens in legumes and their potential synergistic and additive actions, the mechanisms underlying a possible association between legume intake and lower CRC risk might be complex. One of the most important anticancer constituents of legumes is flavonoids, particularly isoflavones. Flavonoids from legumes not only inhibit the growth of tumor cells, but also lead to cell differentiation (Romagnolo and Selmin 2012). Legumes are also rich in dietary fiber, which may increase faecal bulk and thus dilute carcinogenic substances in the gut lumen; decrease gut transit time, which can reduce the time carcinogenic substances are in contact to epithelial cells; delay absorption of complex sugars, and thus reduce postprandial hyperinsulinemia; and increase short-chain fatty acids (SCFA) from bacterial fiber fermentation, which can reduce cell proliferation and facilitate apoptosis (Baena and Salinas 2015). In addition, legumes are good sources of dietary protein, vitamin E, vitamin B, selenium, and lignans with potential cancer-preventive effects. Besides its direct cancer preventive effects, legume consumption may affect disease risk indirectly as well. For example, higher intakes of legumes may replace other sources of protein in the diet such as meat (Zhu, Sun *et al.* 2015).

Flavonoids

Flavonoids are polyphenolic compounds that are distributed widely in the plant kingdom. More than 5,000 individual flavonoids have been identified and classified into more than 10 subgroups according to their chemical structure. They are subdivided into subclasses including flavonols, flavones, flavanones, flavan-2-ols, anthocyanidins, and isoflavones (Jin, Leng *et al.* 2012). Research into their anti-carcinogenic potential with animal and cellular model systems supports a protective role (Barzi, Lenz *et al.* 2013). Epidemiological studies suggest that higher dietary intakes of flavonoids may be associated with lower risk of tumors of the colon (Jin, Leng *et al.* 2012). Possible anticancer mechanisms of flavonoids are inhibition of proliferation, inflammation, invasion, metastasis, and activation of apoptosis (Romagnolo and Selmin 2012). A meta-analysis of 13 case-control studies and 10 cohort studies found that intakes of flavonols, flacan-3-ols, anthocyanidins, and proanthocyanidins were statistically significantly associated with, respectively, 30%, 12%, 32%, and 28% lower risk of colorectal cancer (Woo and Kim 2013). Another recent meta-analysis of eight studies with 390,769 participants suggested that increased intake of flavan-3-ols may be inversely associated with CRC and colorectal adenomas (Jin, Leng *et al.* 2012).

Among legumes, soybeans are particularly rich in isoflavones. The structure of isoflavones is similar to that of endogenous estrogen, and isoflavones can bind to estrogen receptors. There is substantial evidence that the antiestrogenic, anticarcinogenic, anti-inflammatory, and antioxidative properties of isoflavones may favorably influence the risk of several cancers (Akhter, Inoue *et al.* 2008). In human samples, estrogen receptor gene expression was diminished or absent in colorectal tumors, and introduction of an exogenous estrogen receptor gene in cultured colon carcinoma cells resulted in marked growth suppression (Yan,

Spitznagel *et al.* 2010). Epidemiologic data have been mixed. Three studies found that higher intake of isoflavones was associated with 24% to 60% lower risk of colorectal cancer (Seow, Quah *et al.* 2002, Ravasco, Monteiro-Grillo *et al.* 2005, Cotterchio, Boucher *et al.* 2006); Yang et al. reported that a higher intake of isoflavones was borderline statistically significantly associated with 24% lower risk of colorectal cancer (Yang, Shu *et al.* 2009). Oba et al. found no significant association (Oba, Nagata *et al.* 2007).

Legume fiber

In some studies up to a 25% lower cancer risk was found for legume fiber intakes between 33.1 and 12.6 g/day, or a 17% decrease for intakes of 3 times/day (Baena and Salinas 2015). In a recent meta-analysis of four cohort studies, it was found that legume fiber consumption was associated with a 15% lower risk of colorectal cancer (Zhu, Sun *et al.* 2015). The findings from another meta-analysis of four cohort studies found a 11% lower risk of colorectal cancer with higher intake of legume fiber (Aune, Chan *et al.* 2011).

Summary

There have been several epidemiologic studies that investigated an association between overall legume intake or soy intake and colorectal cancer risk, but most were focused on soy foods in Asian countries. Few published studies focused on total legume consumption in United States populations, and their results are very inconsistent. To my knowledge, no study investigated associations of legumes or soy with colorectal adenoma according to adenoma characteristics, which may be part of the reason for the inconsistencies in the past studies. Thus, in my thesis our specific aims are to investigate an association of overall legume and soy consumption with risk for incident, sporadic colorectal adenoma, overall and

according to sex, postmenopausal status and hormone replacement use in women, and adenoma characteristics (multiplicity, colon size, histologic subtype, and degree of dysplasia), in a United States population.

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Manuscript

Legume consumption and incident sporadic colorectal adenoma risk:
A pooled case-control study

By Sijia Ma

Abstract

Purpose: Legumes, especially soy, have multiple potential anti-colon carcinogenic properties. Several studies investigated associations of legumes and soy with colorectal cancer risk, but the results across the studies are inconsistent and few of the studies were conducted in a United States populations.

Methods: We conducted a pooled analysis of data from three colonoscopy-based case-control studies of incident, sporadic colorectal adenoma (pooled n=794 cases and 994 controls) conducted in Minnesota, North Carolina, and South Carolina between 1991 and 2002. Dietary intakes were assessed using semi-quantitative food frequency questionnaires.

Results: The multivariable-adjusted odds ratios (OR) with 95% confidence intervals (CI) for those in the second and third tertiles of total legume consumption relative to those in the lowest were, respectively, 1.18 (CI 0.91 – 1.51) and 1.12 (CI 0.82 – 1.53), and for soy consumption, 1.13 (0.88 – 1.47) and 0.96 (0.71 – 1.28). The ORs and 95% CIs for those above relative to those below the sex-specific median intakes of total legumes and soy in the controls were, respectively, 0.54 (CI 0.24 – 1.19) and 0.96 (CI 0.46 – 2.03) among premenopausal women and 0.89 (CI 0.54 – 1.47) and 0.68 (CI 0.41 – 1.11) among postmenopausal women who took exogenous estrogens.

Conclusion: Our findings provide no support for associations of total legume intake or soy foods intakes overall with risk for incident, sporadic colorectal adenoma, but do suggest the possibility that legume or soy intake may be inversely associated with adenomas among women with a positive estrogen status (i.e. premenopausal or taking exogenous estrogens).

Introduction

Colorectal cancer (CRC) is the third most common cancer diagnosed and the second leading cause of cancer deaths among men and women combined in the United States (American Cancer Society 2014). The age-standardized incidence rate of CRC in Asian countries (e.g., China and Japan) is lower than that in North America and European countries, and the incidence increases substantially in migrants from low-risk to high-risk areas (Center, Jemal *et al.* 2009). Most CRC arise from adenomatous polyps, and adenomas with different characteristics have different risk to become CRC (Tantamango, Knutsen *et al.* 2011). A better understanding of the environmental and genetic risk factors for colorectal adenoma could improve our knowledge of the etiology of CRC and contribute to primary prevention of the disease in high-risk individuals. Dietary intervention has been proposed as a strategy to prevent colorectal tumorigenesis (Pan, Lai *et al.* 2011).

Legumes are a diverse group of foods, including soybeans, peas, beans, chickpeas lentils, peanuts, and other podded plants. A great variety of anti-carcinogens exist in legumes. Flavonoids not only inhibit the growth of tumor cells, but also lead to cell differentiation (Romagnolo and Selmin 2012). Soybeans are particularly rich in isoflavones. The structure of isoflavones is similar to that of endogenous estrogen, and isoflavones can bind to estrogen receptors. There is substantial evidence that the antiestrogenic, anticarcinogenic, anti-inflammatory, and antioxidative properties of isoflavones may favorably influence the risk of several cancers (Akhter, Inoue *et al.* 2008). Besides flavonoids, legumes are good sources of dietary protein, fiber, vitamin E, vitamin B, selenium, and lignans, which may also have anti-cancer effects (Zhu, Sun *et al.* 2015).

Several epidemiologic studies found that a high intake of legumes was associated with a lower risk of CRC, but the results across the studies are inconsistent. Two meta-analysis studies found that legume consumption was inversely associated with risk of colorectal cancer, while Zhu et al. did not find a statistically significant association within the United States population (Wang, Wang *et al.* 2013, Zhu, Sun *et al.* 2015). Another meta-analysis found a 21% lower CRC risk in women who consumed more soy foods, but not in men. No statistically significant association, overall or stratified by sex, was found in Western counties. (Yan, Spitznagel *et al.* 2010). Michels et al. found a lower incidence of colorectal adenomas among women who consumed more legumes. (Michels, Giovannucci *et al.* 2006).

Few published studies focused on total legume consumption in the United States populations, and their results are very inconsistent. To my knowledge, no study investigated associations of legumes with colorectal adenoma according to adenoma characteristics, which may be part of the reason for the inconsistencies in the past studies. Therefore, the current study was conducted to investigate an association of legume consumption with risk for incident, sporadic colorectal adenoma, overall and according to sex, postmenopausal status and hormone replacement use in women, and adenoma characteristics (multiplicity, colon size, histologic subtype, and degree of dysplasia), using data from a pooled, colonoscopy-based, case-control study of incident, sporadic colorectal adenomas in a United States population.

Methods

Case-control studies

Data from three methodologically similar endoscopy-based case-control studies of incident, sporadic colorectal adenomas conducted by the same principal investigator were pooled.

The Cancer Prevention Research Unit study (CPRU) was conducted between 1991 and 1994 as a part of the Minnesota Cancer Prevention Research Unit, an NCI-funded program project that combined several units within the University of Minnesota and Digestive Healthcare, PA (DH), a large multi-clinic private gastroenterology practice (Potter, Bigler et al. 1999). The second case-control study (the Markers of Adenomatous Polyps I (MAP I)) was conducted in community gastroenterology practices in Winston-Salem and Charlotte, North Carolina from 1994-1997 to assess the validity of colonic epithelial cell proliferation as a biomarker of risk for sporadic colorectal adenoma (Boyapati, Bostick *et al.* 2003, Gong, Xie *et al.* 2005). The third case-control study (MAP II) using the same design of MAP I was conducted at Consultants in Gastroenterology, PA, a large and private practice in Columbia, South Carolina in 2002, to investigate associations of the expression patterns of various genes and cell cycle markers in the normal-appearing colorectal mucosa with risk for incident, sporadic adenomas (Daniel, Bostick *et al.* 2009, Sidelnikov, Bostick *et al.* 2009).

Participants were recruited from patients with no history of colorectal neoplasms who were scheduled to undergo outpatient, elective endoscopy for screening or gastrointestinal symptoms at the study sites. Assessment of initial participant eligibility was the same in the three case-control studies. Participants aged 30-74 years who spoke English, had no contraindications for colonoscopy, and had no known genetic syndromes associated with colonic neoplasia or history of inflammatory bowel disease, colorectal adenoma, or cancer

(except non-melanoma skin cancer) were eligible to participate. For CPRU, of the 3,126 colonoscopy patients identified, 2,771 (89%) were eligible on initial screening, and of these, 1,890 (68%) agreed to participate and signed consent. In the MAP I study, 669 (30% of a total of 2,246) colonoscopy patients identified were eligible to participate, and of these, 617 (92%) were contacted and 417 (68%) agreed to participate. In the MAP II study, 305 (87% of a total of 351) colonoscopy patients identified were eligible to participate, and of these, 232 (76%) were contacted and agreed to participate. After excluding participants with hyperplastic polyps, missing status of outcome variable, and those who consumed less than 600 kcal/day or more than 6,000 kcal/day total energy intake, the final sample size for this pooled case-control study included 1,788 participants, among whom 794 were incident, sporadic colorectal adenoma cases and 994 were colonoscopy controls.

Data Collection

Before undergoing colonoscopy, all patients completed mailed questionnaires regarding demographic characteristics, personal medical history, reproductive history (women only), family history of polyps or colon cancer, anthropometrics, diet via a semi-quantitative Willett Food Frequency Questionnaire (Willett, Sampson *et al.* 1988), lifestyle, alcohol and tobacco use, usual physical activity, and reasons for colonoscopy. Preparation for colonoscopy included a 12-hour fast and bowel cleansing with polyethylene glycol. At the clinic visit, the signed consent form and completed questionnaires were collected. The colonoscopy findings were recorded on standardized forms to record colon site and *in vivo* size and shape of any polyps. Upon removal, an index study pathologist using diagnostic criteria established for the National Polyp Study examined polyps histologically (O'Brien, Winawer *et al.* 1990). Only participants with a complete colonoscopy reaching the cecum were eligible. Based on

the colonoscopy and pathology findings, participants were assigned to one of the following three groups: (a) an adenomatous polyp group (defined as either adenomatous or mixed pathology); (b) a hyperplastic polyp-only group; and (c) a colonoscopy-negative control group. Information on adenoma characteristics was collected during verification, including histologic type, location of the largest adenoma, multiplicity, size of the largest adenoma, shape, and degree of atypia of the worst adenoma. Legume consumption was estimated by summing the number of servings per day of all the legumes described below, and soy intake was estimated by summing the number of servings per week of soy foods (tofu, soybeans, and soy milk) included on the food frequency questionnaire. The nine response categories for frequency of intake ranged from "never, or less than once per month" to "6+ per day." Portions sizes were defined as 3-4 oz. for tofu and soybeans, 1/2 cup for string beans, 1/2 cup for peas, or lima beans (fresh, frozen, or canned), 1/2 cup for beans, lentils, chili beans, or garbanzos (baked or dried), 1 cup for bean, pea, or lentil soup, and 8 oz. glass for soy milk. Missing responses for items were coded as never consumed.

Statistical analysis

Prior to analysis, continuous variables with a skewed distribution were log transformed to normalize them. Important covariates, including demographics, lifestyle, and other risk factors were compared between cases and controls using the t-test for continuous variables and the chi-square test for categorical variables.

Study-, sex-specific tertiles of legumes and soy were calculated based on the distribution in the controls. Unconditional logistic regression models were used to assess the association

between legume consumption or soy foods intake and risk of colorectal adenoma. Age, sex, education, family history of CRC in a first degree relative, regular use of NSAIDs and/or aspirin, menopausal status in women, alcohol drinking, smoking, BMI, physical activity, study (CPRU and MAP), total energy intake, red and processed meat, fiber, calcium, vitamin D, fruits, and vegetables were considered as potential confounding variables. Several criteria were used to assess confounding factors: 1) biologic plausibility, 2) whether the variable of interest was associated with the outcome and exposure, 3) whether the logistic regression coefficient of the primary exposure variable substantially changed (by > 10%) after adding the potential confounding variable to the model 4) correlation coefficient < 0.6 between continuous variables. Final covariates included in the minimally-adjusted model were age, sex, total energy, family history of CRC in a first-degree relative, regular use of NSAIDs and/or aspirin, smoking, BMI, hormone replacement therapy use and study (CPRU and MAP). The multivariable-adjusted model included age, sex, total energy, family history of CRC in a first-degree relative, regular use of NSAIDs and/or aspirin, smoking, BMI, hormone replacement therapy use, study (CPRU and MAP), total calcium intake, fruit intake, alcohol drinking, and total red and processed meat intake. In addition, we investigated the associations stratified by potential effect-modifying variables such as sex, regular use of NSAIDs, postmenopausal status, and hormone replacement therapy in women and included the interaction terms in the model and tested the significance of the estimates with the log-likelihood ratio test. We also examined the associations between legumes and adenoma characteristics (multiplicity, size, location, and pathologic subtype).

The associations were expressed as odds ratios with corresponding 95% confidence intervals. A test for trend was calculated based on the median of each tertile of legume

consumption in the model as a continuous variable. All statistical tests were 2-sided, and P values of <0.05 were considered statistically significant. All statistical analyses were conducted with SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

Selected characteristics of cases and controls are shown in table 1. Adenoma cases were more likely to be male, a current smoker, and, if a woman, postmenopausal. On average, cases tended to be older and had greater total energy intakes. Compared to adenoma cases, controls were more likely to have a family history of CRC in a first-degree relative, take NSAIDs regularly (□ ≥ once a week), and, if a women, take HRT. Also, on average, controls had higher intakes of total calcium, vitamin D, and fruits.

The crude and adjusted associations of legumes intake with adenomas are presented in Table 2. There was no definitive pattern in the legume-adenoma association across the tertiles, and none of the point estimates or p-values for trend was statistically significant.

Associations between total legume intake and risk of adenoma according to potential effect modifying risk factors are presented in Table 3. Among those who regularly took a NSAID or aspirin, a greater intake of legumes was associated with higher risk of adenoma, while among those who did not regularly take a NSAID or aspirin, the estimated associations were close to null, although the interaction term was not statistically significant. Because the sample size for analyses stratified on women who were premenopausal, postmenopausal HRT users, and postmenopausal non-HRT users, legume intake was

dichotomized on the median intake among women. Among premenopausal women there was an estimated 46% lower risk of colorectal adenoma among those who consumed more legumes; however, the sample size for this analysis was small and the finding was not statistically significant (OR=0.54, 95% CI: 0.24 - 1.19). Among postmenopausal HRT users there was an estimated non-statistically significant 11% lower risk of adenoma for those who consumed more legumes, and among postmenopausal non-HRT users the estimated association was close to the null (OR 1.04). The associations of legume consumption with adenoma did not differ substantially by sex or family history of colorectal cancer in a first degree relative.

We also examined the crude and adjusted associations of soy intake with colorectal adenomas (Table 4). The estimated associations were close to null and were not statistically significant. The results of the analyses of potential effect modification of the soy intake-adenoma association are presented in Table 5. Unlike for total legume intake, the estimated soy-adenoma association was close to null among premenopausal women. For high vs. low soy intake, risk for adenoma was an estimated 32% lower risk among postmenopausal HRT users, but an estimated 31% higher risk of among postmenopausal non-HRT users; however, none of the point estimates nor the p for interaction were statistically significant.

Associations of legume consumption with adenoma according to adenoma characteristics are shown in Table 6. Among the cases, 32% had at least one adenoma located in the right colon, 33% had multiple adenomas, 32% had an adenoma that was greater or equal than 1 cm in diameter, and 55% had adenomas with moderate or severe dysplasia. The largest or most advanced adenoma had a pedunculated shape in 31% of cases and was of villous or

tubulovillous histology in 28% of cases. The association of legume intake with adenoma did not differ substantially according to adenoma characteristics.

Discussion

Overall, the results from these three pooled case-control studies provide no support for associations of total legume intake or soy foods intake with risk for incident, sporadic colorectal adenoma. The results did suggest the possibility that legume intake may be inversely associated with adenomas among premenopausal women, and to a lesser extent among postmenopausal women who take HRT; however, the sample size for these analyses was small and the findings were not statistically significant.

Legumes are not only rich in protein, but also important sources of dietary fiber, resistant starch, folate, selenium, saponins, protease inhibitors, lectins, phytates, and flavonoids with potential anticancer effects. Possible anticancer mechanisms of flavonoids are inhibition of proliferation, inflammation, invasion, metastasis, and activation of apoptosis (Romagnolo and Selmin 2012). Dietary fiber, which may increase faecal bulk, and thus dilute carcinogenic substances in the gut lumen; decrease gut transit time, which can reduce the time carcinogenic substances are in contact with epithelial cells; delay absorption of complex sugars, and thus reduce postprandial hyperinsulinemia; and increase short-chain fatty acids (SCFA) from bacterial fiber fermentation, which can reduce cell proliferation and facilitate apoptosis (Baena and Salinas 2015). Besides its direct cancer preventive effects, legume consumption may affect disease risk indirectly as well. For example, higher intakes of legumes may replace other sources of protein in the diet such as meat (Zhu, Sun *et al.* 2015). Among legumes, soybeans are particularly rich in isoflavones. The structure of isoflavones is

similar to that of endogenous estrogen, and isoflavones can bind to estrogen receptors. There is substantial evidence that the antiestrogenic, anticarcinogenic, anti-inflammatory, and antioxidative properties of isoflavones may favorably influence the risk of several cancers (Akhter, Inoue *et al.* 2008).

Several epidemiologic studies found that a high intake of legumes or soy foods was associated with a lower risk of CRC, but the results across the studies are inconsistent. A most recent meta-analysis of 14 cohort studies with 1,903,459 participants and 12,261 cases found that a higher intake of legumes was statistically significantly associated with a 10% lower risk of colorectal cancer, but not within the United States population (Zhu, Sun *et al.* 2015). In another meta-analysis, which included 4 cohort and 7 case-control studies, of soy intake and colorectal cancer found a 21% lower colorectal cancer risk among women who consumed higher soy foods, but not in men. No statistically significant association, overall or stratified by sex, was found in Western counties. (Yan, Spitznagel et al. 2010). Consistent with these data, we did not find high intake of total legumes or soy foods to be statistically significant associated with risk of colorectal adenoma overall or stratified by sex. However, another meta-analysis of 3 cohort and 11 case-control studies with a total of 101,856 subjects and 8,380 cases found that a higher intake of legumes was statistically significantly associated with lower risk of colorectal adenoma, including a statistically significant 12% lower risk in populations in the United States (Wang, Wang *et al.* 2013). Michels *et al.* found that women who consumed four or more servings of legumes per week had a 33% lower incidence of colorectal adenomas than did women who consumed one serving per week or less. (Michels, Giovannucci *et al.* 2006).

Previously, epidemiological studies and clinical studies found that colon cancer may be hormonally influenced, as supported by findings that the use of hormone replacement therapy was associated with lower risk for colon or colorectal cancer (Oba, Nagata *et al.* 2007). In human samples, estrogen receptor gene expression was diminished or absent in colorectal tumors, and introduction of an exogenous receptor gene in cultured colon carcinoma cells resulted in marked growth suppression (Issa, Ottaviano *et al.* 1994). Dietary supplementation with isoflavones increased estrogen receptor-**β**expression but reduced estrogen receptor-**α**expression in the colons of female rats(Kramer, Johnson *et al.* 2009). A prospective cohort study in women aged 40-70 found an inverse association of soy consumption with colorectal cancer risk, predominantly among postmenopausal women(Yang, Shu *et al.* 2009). However, a public health center-based prospective study in Japan found no association of colorectal cancer risk with plant estrogens (isoflavones) in postmenopausal women(Akhter, Inoue *et al.* 2008). In our analysis, although the results were not statistically significant, we observed inverse associations of legume intakes with adenoma among women who were premenopausal or were postmenopausal and were on hormone replacement therapy. Similarly, we also observed an inverse association of soy foods with adenoma among postmenopausal women who were on hormone replacement therapy, but again the results were not statistically significant.

In a number of population-based studies, a 40 – 50% lower risk of colorectal cancer was found in persons who regularly use aspirin and other NSAIDs (Asano and McLeod 2004, Chan, Giovannucci *et al.* 2005, Chan 2013). Randomized secondary prevention and primary prevention trials in high-risk patients have clearly demonstrated that NSAID treatment caused regression of preexisting adenomas (Herendeen and Lindley 2003). To our

knowledge, no reported studies of human have investigated the joint associations of legumes intake or soy foods intake and NSAID use with colorectal adenomas incidence or recurrence. Inconsistent with synergistic effects of high intake of legumes and regular use of NSAID or aspirin, we found higher risk of adenoma associated with higher intake of legumes among people who regularly used NSAID or aspirin. One explanation could be chance, particularly considering the small sample size and wide confidence intervals.

This study had some limitations. First, because most of the participants were white (> 95%), the results from this analysis may not be generalizable to other racial or ethnic groups. Second, the colonoscopy control group represents a highly selected group of participants. These individuals may have been at higher risk and thus more similar to the cases, since participants in these groups had an indication for colonoscopy. In our study, controls were more likely to have a history of colorectal cancer in a first degree relative than did cases, which may have biased our results, although most likely toward the null. There may have been insufficient heterogeneity of legume and soy exposure in our population to detect an association. Third, although this pooled study had 794 colorectal adenoma cases and 994 controls, the sample size was still small for some subgroup analyses.

The main strengths of this study was that all endoscopy-negative controls went through a complete colonoscopy and were found to be polyp free, thus decreasing the possibility of outcome misclassification bias, and information on multiple covariates was collected before outcome status was ascertained to reduce recall bias.

In conclusion, the results from this study provide no support for an overall association of total legume intake or soy foods intake with risk for incident, sporadic colorectal adenoma. However, our findings did suggest the possibility that legume or soy intake may be inversely associated with adenomas among women with a positive estrogen status (i.e., premenopausal or taking exogenous estrogens); however, given that the sample size for these analyses was small and the findings were not statistically significant, further study is needed.

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Tables

Table 1. Selected Characteristics of Cases and Controls in Three Pooled Case-Control Studies of Incident, Sporadic Colorectal Adenomas; United States, 1991-2002

Characteristics	Cases	(n=794)	Controls	(n=994)	P values[a]
	Mean (SD)	%	Mean (SD)	%	
Age, years	58.1 (9.3)		53.6 (10.6)		<0.01
Male		61		37	<0.01
White		96		95	0.38
Bachelor's degree or higher		28		30	0.59
Family history[b]		16		30	<0.01
NSAID use[c]		15		25	<0.01
Alcohol drinking		67		64	0.16
Postmenopausal (women only)		84		72	<0.01
HRT user (women only)[d]		48		55	0.06
Current smoker		24		15	<0.01
BMI, kg/m^2	27.6 (5.2)		27.2 (5.4)		0.08[e]
Physical activity, MET-hours/week	242.2 (249.2)		222.2 (196.6)		0.71[e]
Dietary intake per day					
Total energy, kcal	2,072 (779)		1,961 (729)		<0.01[e]
Red and processed meats, servings	7.6 (6.7)		6.9 (6.1)		0.12[e]
Dietary fiber, g	21.6 (9.5)		21.7 (14.6)		0.38[e]
Dietary legumes, servings	1.0 (1.4)		1.0 (1.5)		<0.01[e]
Total calcium, mg[f]	907.8 (510.1)		957.7 (589.5)		0.07[e]
Total vitamin D, IU[f]	324.5 (258.5)		339.9 (287.9)		0.60[e]
Total soy, servings per week	3.1 (2.7)		3.2 (3.1)		0.90[e]
Total fruit, servings per week	13.1 (12.3)		14.0 (12.3)		0.02[e]
Total vegetables, servings per week	20.2 (16.3)		20.9 (17.3)		0.24[e]

Abbreviations: NSAID, non steroidal anti inflammatory drug; HRT, hormone replacement therapy; BMI, body mass index; MET, metabolic equivalent of task; SD, standard deviation.

a. P value for comparing cases and controls; by chi-square test for categorical variables and t test for continuous variables.
b. Family history of colorectal cancer in first-degree relative.
c. At least once per week.
d. Ever on hormone replacement therapy, in women.
e. Log transformation used to normalize the variable.
f. From diet plus supplements.

Table 2. Crude and Adjusted Associations of Legume Intake with Incident, Sporadic Adenomas in Three Pooled Case-Control Studies of Incident Colorectal Adenomas; United States, 1991-2002

Legume intake	Crude		Model 1[a]		Model 2[b]	
Tertile	OR	95% CI	OR	95% CI	OR	95% CI
1	1.00		1.00		1.00	
2	1.27	(1.02, 1.58)	1.20	(1.02, 1.67)	1.18	(0.91, 1.15)
3	1.27	(0.99, 1.65)	1.12	(0.96, 1.75)	1.12	(0.82, 1.53)
P trend[c]	0.14		0.72		0.68	

Abbreviations: OR, odds ratio; CI, confidence interval; CRRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps.
a. Model 1 adjusted for age, sex, total energy, family history of colorectal cancer in a first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, smoking, body mass index, hormone replacement therapy use, and study (CPRU, MAP).
b. Model 2 adjusted for age, sex, total energy, family history of colorectal cancer in a first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, smoking, body mass index, hormone replacement therapy use, total calcium intake, fruit intake, alcohol intake, total red and processed meat intake, and study (CPRU, MAP).
c. Ptrend values (2-sided) were calculated by including the median of each tertile of legumes as a continuous variable in addition to all above-mentioned covariates in model 1 and model 2.

Table 3. Multivariable-adjusted Associations of Legume Intake with Incident, Sporadic Adenomas, Stratified on Sex, Family History, NSAID Use, Postmenpausal Status (women only), and HRT User (women only) in Three Pooled Case-Control Studies of Incident Colorectal Adenomas; United States, 1991-2002

Adenoma and legume intake	No. of cases	No. of controls	OR[a]	95% CI[a]	$P_{interaction}$
Sex					0.25
Male					
1	134	123	1.00		
2	217	168	1.02	(0.72, 1.45)	
3	127	74	1.24	(0.80, 1.93)	
P trend[b]			0.29		
Female					
1	93	213	1.00		
2	156	268	1.40	(0.97, 2.03)	
3	57	135	1.01	(0.63, 1.62)	
P trend[b]			0.62		

Family history[c]					0.95
Yes					
1	37	91	1.00		
2	54	135	0.91	(0.50, 1.65)	
3	32	70	1.24	(0.61, 2.50)	
P trend[b]			0.43		
No					
1	192	246	1.00		
2	322	300	1.25	(0.94, 1.65)	
3	152	144	1.07	(0.75, 1.52)	
P trend[b]			0.97		
Regular use of NSAID or aspirin[d]					0.09
Yes					
1	32	94	1.00		
2	53	105	1.67	(0.89, 3.13)	
3	32	51	2.17	(1.01, 4.65)	
P trend[b]			0.08		
No					
1	199	245	1.00		
2	320	333	1.08	(0.82, 1.43)	
3	152	162	0.97	(0.69, 1.38)	
P trend[b]			0.88		
Premenopausal women					0.15
1	34	107	1.00		
2	13	67	0.54	(0.24, 1.19)	
Postmenopausal women with HRT use					
1	79	161	1.00		
2	51	124	0.89	(0.54, 1.47)	
Postmenopausal women without HRT use					
1	70	90	1.00		
2	47	50	1.04	(0.57, 1,90)	

Abbreviations: OR, odds ratio; CI, confidence interval; HRT, hormone replacement therapy; NSAID, nonsteroidal antiinflammatory drug; CPRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps.

a. Odds ratios with 95% confidence intervals was adjusted for age, sex, total energy, family history of colorectal cancer in a first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, smoking, body mass index, hormone replacement therapy use, total calcium intake, fruit intake, alcohol intake, total red and processed meat intake, and study (CPRU,MAP). A stratification variable was not included in the model.

b. Ptrend values (2-sided) were calculated by including the median of each tertiles of legumes as a continuous variable in addition to all below-mentioned covariates in the multivariable models.

c. Family history of colorectal cancer in first-degree relative.

d. At least once per week.

Table 4. Crude and Adjusted Associations of Soy Intake with Incident, Sporadic Adenomas in Three Pooled Case-Control Studies of Incident Colorectal Adenomas; United States, 1991-2002

Soy intake and Tertile	Crude		Model 1[a]		Model 2[b]	
	OR	95% CI	OR	95% CI	OR	95% CI
1	1.00		1.00		1.00	
2	1.12	(0.89, 1.39)	1.16	(0.90, 1.50)	1.13	(0.88, 1.47)
3	0.97	(0.77, 1.22)	0.94	(0.71, 1.26)	0.96	(0.71, 1.28)
P trend[c]	0.64		0.53		0.62	

Abbreviations: OR, odds ratio; CI, confidence interval; CRRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps.
a. Model 1 adjusted for age, sex, total energy, family history of colorectal cancer in a first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, smoking, body mass index, hormone replacement therapy use, and study (CPRU, MAP).
b. Model 2 adjusted for age, sex, total energy, family history of colorectal cancer in a first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, smoking, body mass index, hormone replacement therapy use, total calcium intake, fruit intake, alcohol intake, total red and processed meat intake, and study (CPRU, MAP).
c. Ptrend values (2-sided) were calculated by including the median of each tertile of legumes as a continuous variable in addition to all above-mentioned covariates in model 1 and model 2.

Table 5. Multivariable-adjusted Associations of Soy Intake with Incident, Sporadic Adenomas, Stratified on Sex, Family History, NSAID Use, Postmenpausal Status (women only), and HRT User (women only) in Three Pooled Case-Control Studies of Incident Colorectal Adenomas; United States, 1991-2002

Adenoma and Soy intake	No. of Cases	No. of Controls	OR[a]	95% CI[a]	P interaction
Sex					0.41
Male					
1	161	142	1.00		
2	182	117	1.29	(0.90, 1.85)	
3	135	106	0.96	(0.63, 1.46)	
P trend[b]			0.69		
Female					
1	110	207	1.00		
2	106	218	0.97	(0.66, 1.41)	
3	90	191	0.93	(0.62,1.41)	
P trend[b]			0.75		
Family history[c]					0.77
Yes					
1	38	98	1.00		
2	48	108	0.94	(0.52, 1.71)	
3	37	90	0.91	(0.46, 1.81)	
P trend[b]			0.81		
No					

1	235	254	1.00		
2	245	228	1.19	(0.89, 1.58)	
3	186	208	0.95	(0.69, 1.31)	
P trend[b]			0.60		
Regular use of NSAID or aspirin[d]					0.93
Yes					
1	34	81	1.00		
2	50	95	1.29	(0.70, 2.38)	
3	33	74	0.92	(0.44, 1.91)	
P trend[b]			0.70		
No					
1	240	271	1.00		
2	242	243	1.11	(0.83, 1.47)	
3	189	226	0.97	(0.70, 1.33)	
P trend[b]			0.83		
Premenopausal women					0.08
1	27	96	1.00		
2	20	78	0.96	(0.46, 2.03)	
Postmenopausal women with HRT use					
1	79	153	1.00		
2	51	132	0.68	(0.41, 1.11)	
Postmenopausal women Without HRT use					
1	68	85	1.00		
2	49	55	1.31	(0.72, 2.39)	

Abbreviations: OR, odds ratio; CI, confidence interval; HRT, hormone replacement therapy; NSAID, nonsteroidal antiinflammatory drug; CPRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps.

a. Odds ratios with 95% confidence intervals was adjusted for age, sex, total energy, family history of colorectal cancer in a first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, smoking, body mass index, hormone replacement therapy use, total calcium intake, fruit intake, alcohol intake, total red and processed meat intake, and study (CPRU,MAP). A stratification variable was not included in the model.

b. Ptrend values (2-sided) were calculated by including the median of each tertiles of legumes as a continuous variable in addition to all below-mentioned covariates in the multivariable models.

c. Family history of colorectal cancer in first-degree relative.

d. At least once per week.

Table 6. Multivariable-adjusted Associations of Legume Intake with Incident, Sporadic Adenomas, Stratified on Adenoma Characteristics in Three Pooled Case-Control Studies of Incident, Sporadic Colorectal Adenomas; United States, 1991-2002

Adenoma Characteristic and Tertiles of Legume Intake	No. of Cases	No. of Controls	OR[a]	95% CI[a]
Location				
Right colon[b]				
1	78	342	1.00	
2	121	438	1.14	(0.79, 1.66)
3	58	214	1.11	(0.69, 1.78)
P trend[c]			0.78	
Left colon[d]				
1	179	342	1.00	
2	315	438	1.22	(0.94, 1.60)
3	150	214	1.12	(0.80, 1.57)
P trend[c]			0.76	
Multiplicity				
Multiple adenomas				
1	71	342	1.00	
2	127	438	1.28	(0.88, 1.88)
3	59	214	1.30	(0.80, 2.10)
P trend[c]			0.42	
Single adenoma				
1	156	342	1.00	
2	244	438	1.11	(0.84, 1.46)
3	123	214	1.05	(0.74, 1.49)
P trend[c]			0.90	
Size[e]				
Large adenoma				
≥ 1 cm				
1	71	342	1.00	
2	120	438	1.09	(0.75, 1.59)
3	59	214	1.15	(0.72, 1.84)
P trend[c]			0.59	
Small adenoma				
< 1cm				
1	161	342	1.00	
2	257	438	1.20	(0.90, 1.58)
3	126	214	1.13	(0.80, 1.61)
P trend[c]			0.68	
Shape				
Pedunculated				
1	58	342	1.00	
2	83	438	0.94	(0.62, 1.43)
3	46	214	1.05	(0.62, 1.75)
P trend[c]			0.79	
Sessile				
1	128	342	1.00	
2	216	438	1.26	(0.94, 1.71)
3	113	214	1.32	(0.91, 1.92)

P trend[c]			0.24	
Histologic type				
Villous or tubulovillous				
1	65	342	1.00	
2	107	438	1.12	(0.76, 1.67)
3	41	214	0.95	(0.56, 1.62)
P trend[c]			0.73	
Tubular				
1	162	342	1.00	
2	262	438	1.15	(0.87, 1.51)
3	141	214	1.16	(0.82, 1.63)
P trend[c]			0.52	
Degree of atypia of the worst adenoma				
Mild				
1	80	342	1.00	
2	156	438	1.24	(0.88, 1.75)
3	97	214	1.37	(0.92, 2.04)
P trend[c]			0.19	
Moderate/Severe				
1	137	342	1.00	
2	210	438	1.16	(0.86, 1.56)
3	81	214	0.94	(0.63, 1.40)
P trend[c]			0.58	

Abbreviations: OR, odds ratio; CI, confidence interval; CPRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps;

a. Odds ratios with 95% confidence intervals were adjusted for age, sex, total energy, family history of colorectal cancer in a first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, smoking, body mass index, hormone replacement therapy use, total calcium intake, fruit intake, alcohol intake, total red and processed meat intake, and study (CPRU,MAP)

b. At least one adenoma in the right colon, which includes the cecum, ascending colon, hepatic flexure, and transverse colon.

c. Ptrend values (2-sided) were calculated by including the median of each tertiles of legume intake as a continuous variable in addition to all above-mentioned covariates in the multivariable model.

d. At least one adenoma in the left colon, which includes the splenic flexure, descending colon, sigmoid colon, and rectum.

e. Adenoma size from in vivo comparison of maximum diameter to fully opened endoscope forceps.