Chapter 7

Grain Legume Consumption Inhibits Colorectal Tumorigenesis: A Meta-Analysis of Human and Animal Studies

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Additional information is available at the end of the chapter

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Abstract

Grain legume consumption has been linked in meta-analysis studies to decreased risk of metabolic syndrome, obesity, and cardiovascular diseases; however, the evidence for a chemo-protective effect of grain legume consumption against colorectal tumorigenesis has been considered inconclusive. We conducted a meta-analysis of human and animal studies to evaluate the effect of grain legume consumption on colorectal cancer (CRC) and its precursors. Twelve case-control studies (42,473 controls and 12,408 cases) and 11 prospective cohorts (1,533,527 participants including 12,274 cases) were included in the meta-analysis; the pooled risk ratio (95% confidence interval) for the highest versus the lowest legume intake group based on a random effects model was 0.72 (0.60–0.89) for incident adenoma, 0.91 (0.84–0.99) for prevalent adenoma, and 0.82 (0.74–0.91) for CRC. Fourteen animal studies (355 animals on grain legume diets and 253 animals on control diets) were included in the meta-analysis and showed in all but one study a chemo-preventive effect against colorectal tumorigenesis. Grain legumes contain various compounds (e.g., resistant starch, soluble fiber, insoluble fiber, phytosterols, saponins, phytates, flavonoids, proanthocyanidins, and phenolic acids) that have been shown to inhibit colorectal tumorigenesis in animal studies at concentrations that are relevant for human diets. Grain legume consumption alters several molecular pathways (e.g., p53, mTOR, NF-kB, Akt, and AMPK) that are critical for tumor induction, promotion, and progression. Based on our meta-analysis, daily grain legume consumption confers chemo-preventive effects against CRC.

Keywords: grain legumes, colorectal cancer, meta-analyses, bioactive compounds, molecular mechanisms

1. Introduction

Grain legumes (i.e., pulses) are defined as plants belonging botanically to the family *Leguminosae*, which are harvested as dry seeds for food consumption [1–3]. Grain legumes are behind cereal grains the most common food crop worldwide; the primarily grown grain legumes are in the order as follows: dry beans (e.g., pinto, navy, red kidney, lima, butter, white, and black beans; *Phaseolus and Vigna* ssp.), chick peas (i.e., garbanzo beans; *Cicer arietinum*), dry peas (e.g., garden peas; *Pisum sativum*), dry cow peas (*Vigna unguiculata*), lentils (*Lens culinaris*), and dry broad beans (e.g., horse beans; *Vicia faba*) [3–5]. Beans are oval or kidney shaped, peas are round, and lentils are flat. Grain legumes have served as staple foods in many cultures around the globe, as they can be grown relatively inexpensively in various climate zones and have a health-promoting nutrient profile, that is, they are a good dietary source of protein, rich in fiber and folate, and very low in saturated fatty acids, cholesterol, and sodium [6–8].

Grain legume consumption dramatically decreased in westernizing countries [9] and is in the U.S., similar to other Western countries [10, 11], on average low (12.9 g/d) and infrequent (only 8 and 14% consumed grain legumes daily or every other day) [6, 12]. Given the health-promoting properties and nutrient profile of grain legumes and the growing interest in ethnic, gluten-free, and vegetarian cuisine in Western countries, increasing grain legume consumption represents an important public health opportunity for chronic disease prevention.

A research focus is the use of legumes for cancer prevention, specifically colorectal cancer (CRC) [4]. Globally, CRC is the third most common cancer in men and the second most common in women [13]. Two recent A meta-analysis study reported a protective effect of legume consumption for colorectal adenomas (CRAs) in case-control and cohort studies (combined odds ratio (OR) = 0.83; 95% confidence interval (CI): 0.75–0.93) and CRC in cohort studies (OR = 0.91; 95% CI: 0.84–0.98) [14, 15]. Both meta-analysis studies, however, included studies in which participants consumed legumes primarily as soy products (i.e., studies conducted in China, Japan, Malaysia, and South Korea), as opposed to grain legumes (i.e., studies conducted in Africa, North and South America, and Europe). Moreover, the meta-analysis of CRC showed a protective effect for soybeans (OR = 0.85; 95% CI: 0.73–0.99) but not for other beans (OR = 1.00; 95% CI: 0.89–1.13) [15]. A third meta-analysis study published in 2010 reported no statistically significant association between legume fiber consumption and CRC in four prospective U.S. and European studies combined (OR = 0.89; 95% CI: 0.78–1.02) [16].

The objective of this chapter is to evaluate the evidence of a chemo-preventive role of grain legume consumption in colorectal tumorigenesis in human (ecological, case-control, and cohort studies) and animal studies by conducting a literature review and meta-analyses. The goal is to suggest areas of future research and provide up-to-date scientific evidence for dietary recommendation of legume consumption.

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2. Colorectal cancer: incidence, mortality, and risk factors

Worldwide, annually 1.361 million new CRC cases and 0.694 million deaths due to CRC accrue, according to GLOBOCAN in 2012 [13, 17]. In the U.S., the lifetime risk of being diagnosed with CRC is 5% and the treatment costs were estimated to be over $14 billion [18, 19], highlighting CRC prevention as a public health priority. CRC development is a multistep process over many years, often decades, involving usually random genetic mutations in colorectal epithelial cells causing the activation of tumor-promoting genes and the loss of tumor suppressor gene function [20, 21]. Starting often as aberrant crypt foci (ACF), most CRC arise from benign, adenomatous polyps (i.e., adenomas) that grow from glandular cells of the colorectal epithelial lining into advanced adenomas and then adenocarcinomas [22–24]. Over 50% of the Western population will develop colorectal adenomas (CRAs) by the age of 70 [23]. Less than 10% of adenomas, however, progress to become invasive and spread to adjacent blood or lymph vessels [25]. Success of CRC treatment depends on early detection. If CRC has not spread beyond the colorectal wall (i.e., localized stage), 5-year survival rates are 90.3%; however, survival rates decline when CRC has spread to lymph nodes and/or nearby tissue (i.e., regional disease; a 5-year survival of 70.4%) and are low when CRC has spread to other organs (i.e., distant disease; a 5-year survival of 12.5%) [26]. Currently, only 40% of CRC patients are diagnosed with localized stage, highlighting that importance of early detection and treatment of CRC and its precursors [27].

Genetics is an important CRC risk factor. About 20% of CRC patients have a family history of CRC (10–15% lifetime risk for patients with one first-degree relative; 20% lifetime risk for patients with at least two first-degree relatives or one first-degree relative diagnosed with CRC before age 45) and 2–4% have a well-defined genetic syndrome (i.e., Lynch syndrome and familial polyposis; 80–90% lifetime risk) [19]. Chronic inflammation, specifically inflammatory bowel disease (IBD), is another important CRC risk factor with a 10–20% lifetime risk, which is increased among patients with a longer IBD history [19, 28]. Other important medical CRC risk factors are obesity, insulin resistance, and diabetes mellitus; CRC risk increases linearly with duration and severity of those morbidities [19, 29–33]. Modifiable CRC risk factors include smoking, heavy alcohol consumption, and sedentary behavior, each with a 6% lifetime risk [19], whereas medications such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) and hormone-replacement therapy in postmenopausal women can decrease CRC risk [19].

Food and nutrition play an important part in the etiology and prevention of CRC and may account for 70–90% of all cases [34–36]. A panel of experts, primarily epidemiologists organized by the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR), evaluated the scientific evidence on food, nutrition, and physical activity on cancer risk [34]. Human studies were ordered according to the quality of the study design as follows: (1) ecological studies (lowest quality; most susceptible to confounders; i.e., factors that are associated with both disease status and the evaluated food); (2) case-control studies (very susceptible to recall bias; i.e., selective reporting of the diet after disease diagnosis); (3) Prospective cohort studies; and (4) clinical trials (gold standard and least susceptible to bias). In the case of substantial amount of evidence available, the panel focused on studies using

high-quality designs. Evidence from animal and cell culture studies was taken into account to demonstrate plausible mechanism for diet and cancer association. Based on the evidence, an individual food, food group, or individual nutrient was classified for each cancer site as "convincing", "probable", "limited-suggestive", or "limited-no conclusion" decreases the risk or increases the risk [34].

In 2007, the panel classified red and processed meat consumption as convincingly increases CRC risk, whereas calcium and foods containing fiber were classified as probably decreases CRC risk, and selenium and foods containing folate were classified as limited-suggestive evidence for decreasing CRC risk [34]. No conclusion was made for legumes and CRC risk because of the limited data available in 2007 [34]. As in the last 8 years more data have been collected, we reevaluate in this chapter the evidence on the relation between grain legume consumption and CRC risk. We hypothesized a protective effect of grain legume consumption on CRC risk because grain legumes are an excellent dietary source of fiber (5.7–9.0 g/100 g of cooked legumes) and folate (83–174 μg/100 g of cooked legumes) [7], both of which were classified as decreasing CRC risk in 2007 [34].

3. Grain legumes and colorectal neoplasia in human studies

Ecological studies examine the association between diet and disease on the population level; five studies evaluated the relation between legume intake and risk of CRC incidence or mortality on the population level and observed inconsistent relations [9, 37–40]. Correa reported that countries with higher bean consumption in 1964–1966 had lower colon cancer mortality rates 7–9 years later ($r = -0.68$) [40]. Similarly, Bejar *et al*. stated that the decrease in legume consumption between 1960 and 1990 coincided with an increase in CRC incidence and mortality rates 10 years later in Spain [37, 39]. In follow-up studies, Bejar *et al*. extended the analysis to 15 European and 13 non-European countries [9, 38]. Whereas the strong inverse relation between legume intake and CRC incidence rates held true for some countries (i.e., Norway, Spain, Germany, and France), other countries (i.e., Australia, Italy, and Colombia) had positive relations, as a result of a slight increase in legume consumption between 1965 and 2005. Thus, changes in legume consumption alone cannot explain the temporal changes in CRC incidence rates; rather, changes toward a Western diet were associated with an increased CRC risk (depending on country of origin, adoption of a westernized diet either increased or decreased grain legume consumption). In support, Monroe *et al*. reported in a migrant study that an increase of CRC incidence rates (men: 85%; women: 95%) coincided with a 46% decrease in dry bean or pea consumption (57.0–26.6 g/d) from first- to second-generation Mexico-born U.S. Americans in the Multiethnic Cohort Study [41], and Haentzel *et al*. showed a detrimental effect of grain legume consumption on CRC incidence in Japan-born Hawaiian [42].

In case-control studies, participants with (cases) or without (controls) a disease recall their diet. Besides recalling a diet from past years, participants try to make sense of their disease outcome based on their lifestyle choices. Thus, foods and food groups that have been known to be associated with disease outcomes by the public are often erroneously associated with the

disease outcome (i.e., selective reporting bias). Nineteen peer-reviewed publications (46,769 controls and 14,567 cases; two studies had each two publications [43, 44] and [45, 46]) evaluated in 17 case-control studies the relation between legume consumption and colorectal neoplasia; six studies reported prevalent adenomas as endpoint [47–52] and 11 studies reported carcinomas as endpoint [42–46, 53–60] (**Table 1**). Most case-control studies were from the U.S. (n = 8), five were from Europe, two were from South America, and one each from Australia and Jordan. Risk estimates specific to the intake of legumes (including soybeans and their products), grain legumes, and grain legume fiber were reported in six, 11, and two case-control studies, respectively. Gender-specific risk estimates were reported in five case-control studies, and cancer-site–specific risk estimates were reported for colon and rectum in seven and four case-control studies, respectively. Half of the studies showed a protective legume effect on CRA (**Table 1**), one of which was statistically significant [50]. A distinct clustering was observed for CRC. Seven of 11 case-control studies had significant risk estimates of 0.5 or lower [45, 46, 50, 53, 55, 56, 59, 60]; three of the six low-risk estimates were from women and, for the remaining three, no gender-specific risk estimates were reported. In contrast, the risk estimates of the other studies were around 0.9 (**Table 1**).

Reference, region (country)	Study period	Study design, no. controls/cases	Sex, age	Diet assessment	Grain legume, quantity for comparison, risk estimates (95% CI)	Matching/adjusting for confounders
Prevalent colorectal adenoma						
Sandler et al., 1993 [47] North Carolina (U.S.)	1988–1990	Colonoscopy Cases: 236 Controls: 409	Both, ≥30 years, no CRC, IBD history	Phone interview: FFQ with >100 food items for previous yr	Grain legume fiber Men: ≥3.14 vs. <0.97 g/d OR = 0.99 (0.43–2.29) Women: ≥2.17 vs. <0.61 g/d OR = 1.26 (0.63–2.51)	No matching specified Adjusted for age, alcohol intake, BMI, and total energy intake
Witte et al., 1996 [48] California (U.S.)	1991–1993	Sigmoidoscopy Cases: 488 Controls: 488	Both 50–74 years; no CRA, IBD history	Personal interview: FFQ with 126 food items for previous yr	Legumes (beans, lentils, peas, lima beans, tofu, soybeans, peanut butter) Mean 8.5 vs. 0.5 servings/wk OR: 0.85 (0.56–1.28)	Matched by age, sex, day of sigmoidoscopy, Kaiser center Adjusted by race, BMI, physical activity, smoking, and intake of total energy and saturated fat
Smith-Warner et al., 2002 [49] Minnesota Cancer Prevention Research Unit Study (U.S.)	1991–1994	Colonoscopy and population Cases: 564 Controls: 682 colonoscopy, 535 population	Both, 30–74 years, no CRA, IBD history	Self-administered FFQ precolonoscopy with >153 food items for previous yr	Legumes (alfalfa sprouts, beans, peas) Men: Mean 5.0 vs. 1.0 servings/wk Colonoscopy: OR = 0.96 (0.62–1.49) Population: OR = 1.15 (0.77–1.72) Women: Mean 5.5 vs. 1.1 servings/wk Colonoscopy: OR = 1.08 (0.68–1.74) Population: OR = 0.96 (0.58–1.59)	Matched by age, sex, and residence Adjusted for age, total energy and fat intake, BMI, smoking, alcohol, NSAID use, multivitamin use, and hormone replacement therapy
Agurs-Collins et al., 2006 [50] African-American (U.S.)	2001–2003	Colonoscopy Cases: 53 Controls: 133	Both, 29–81 years	FFQ with 39 food items (Rate Your Diet Quiz)	Grain legumes (dry beans, split peas, lentils) ≥3× vs. ≤1×/wk OR = 0.19 (0.04–0.91)	No matching specified Adjusted for age, smoking, alcohol, sex, weight, aspirin use, alcohol, family CRC history, and exercise
Millen et al., 2007 [51] Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)	1993–2001	Sigmoidoscopy Cases: 3057 Controls: 29,413	Both, 55–74 years; no CRA, IBD history	Self-administered FFQ pre-, on, or post-sigmoidoscopy with 137 food items for previous yr	Legumes (beans, peas, tofu, and soybeans) Median 0.4 vs. 0.05 energy-adjusted servings/wk OR = 0.92 (0.81–1.03) Sex and age adjusted: OR = 0.85 (0.75–0.96)	Matching not specified Adjusted for age, sex, race, education, family CRC history, smoking, alcohol use, aspirin use, replacement hormone use, physical activity, BMI
Wu et al., 2009 [52] Tennessee Colorectal Polyp Study (U.S.)	2003–2005	Colonoscopy Cases: 764 Controls: 1517	Both, 40–75 years, no CRA, IBD history	FFQ with >108 food items for previous yr	Grain legumes (green beans and peas, dry and canned beans) Tertile T3 vs. T2 Quantity N/A OR = 0.95 (0.74–1.24)	No matching specified Adjusted for age, sex, race, study location, BMI, smoking, alcohol consumption, NSAID use, physical activity, education level, family income, family CRC history, and intake or total energy and red meat

Reference, region (country)	Study period	Study design, no. controls/cases	Sex, age	Diet assessment	Grain legume, quantity for comparison, risk estimates (95% CI)	Matching/adjusting for confounders
Colon Cancer						
Iscovich et al., 1992 [56] La Plata (Argentina)	1985–1987	Population Cases: 110 Controls: 220	Both, 35–80 years	Personal interview FFQ with 140 food items for previous 5 yrs	Grain legumes (beans, lentils, peas, and chick peas) Quartile 4 vs. 1 OR = 0.52 (0.24–1.12) Quartile 3 vs. 1 OR = 0.32 (0.14–0.73) Quantity N/A	Matched by age and gender Adjustment not specified
Steinmetz et al., 1993 [60] Adelaide (Australia)	1979–1980	Population Cases: 220 Controls: 438	Both, 30–74 years	Self-administered FFQ with 141 food items a yr ago	Legumes (green, dry and broad beans, lentils, dry and chick peas, and soybeans) Men: >1 vs. 0 servings/wk OR = 0.74 (0.38–1.45); Women: >0.6 vs. 0 servings/wk OR = 0.43 (0.20–0.93)	Matched by age and gender Adjusted for protein intake, occupation, Quetelet's index, alcohol consumption, and age at first live birth (only women)
Kampman et al., 1995 [57] (Netherlands)	1989–1993	Population Cases: 232 Controls: 259	Both, ≤75 years, no history of CR tumors	Personal interview: FFQ with 289 food items for previous yr	Legumes Quartile 4 vs. 1 (infrequent legume consumption) OR = 1.08 (0.67–1.76)	Matched by age, gender, and degree of urbanization Adjustment not specified
Colorectal Cancer						
Haenszel et al., 1973 [42] Hawaiian born in Japan (U.S.)	1966–1970	Hospital Cases: 179 Controls: 357	Both Age N/A	Personal interview: four legumes, soybeans excluded	Grain legumes (green and red beans, peas, and Chinese peas) >21× vs. <8×/mo legumes RR = 3.5 95% CI N/A	Matched by sex and birth place Adjustment not specified
La Vecchia et al., 1988 [58] Milan (Northern Italy)	1985–1987	Hospital Cases: 339 colon, 236 rectal Controls: 778	Both, <75 years	Personal interview: 29 food items prior to disease diagnosis	Grain legumes Tertile 3 vs. 1 Quantity N/A Colon: RR = 1.04; Rectum: RR = 0.94 95% CI N/A	Matching not specified Adjusted for social class, age, sex, and area of residence
Benito et al., 1991 [53] Majorca (Spain)	1984–1988	Population and Hospital Cases: 286 Controls: 203 hospital 286 population	Both, <80 years	Personal interview: FFQ with 99 food items for previous yr	Grain legume fiber Quartile 4 vs. 1 Quantity N/A RR = 0.40 95% CI N/A	Matched by age and gender Adjusted for age, sex, body weight, and total energy intake
Bidoli et al., 1992 [54] Pordenone (North Eastern Italy)	1986–1990	Hospital Cases: 123 colon, 125 rectal Controls: 699	Both Age not specified	Personal interview: FFQ (number of food items N/A before disease) onset	Grain legumes Tertile 3 vs. 1 Quantity N/A Colon: RR = 1.2 Rectum: RR = 0.8 95% CI N/A	Matched by hospital Adjusted for age, gender, and social status
Le Marchand et al., 1997 [59] Hawaii Multiethnic (U.S.)	1987–1991	Population Cases: 1192 Controls: 1192	Both <85 years, no history of colorectal tumors	Personal interview: FFQ with 282 food items 3 yrs before disease onset	Legumes (including soy products) Men: >46 vs. <11 g/d OR = 0.8 (0.5–1.2) Women: >44 vs. <9 g/d OR = 0.5 (0.3–0.9)	Matched by age, sex, and race Adjusted for age, family CRC history, alcohol consumption, smoking, physical activity, Quetelet index, and intake of total calories, eggs, and calcium
Franceschi et al., 1998 [55] (Italy)	1991–1996	Hospital Cases: 1225 colon 728 rectal Controls: 5155	Both Age not specified	Personal interview: FFQ with 98 food items 2 yrs before disease diagnosis	Grain legumes (beans and peas) >3 vs. <0.5 servings/wk Colon: OR = 0.5 (0.4–0.7) Rectum: OR = 0.7 (0.5–0.9)	Matching not specified Adjusted for age, sex, center, year of interview, education, physical activity, alcohol consumption, and total energy intake
Deneo-Pellegrini et al., 2002 [46] Montevideo (Uruguay)	1996–2002	Hospital Cases: 484 Controls: 1452	Both 30–89 years	Personal interview: FFQ with 64 food items a yr before disease diagnosis	Grain legumes (kidney beans and lentils) Quartile 4 vs. 1 Quantity N/A Overall: OR = 0.7 (0.5–0.9) Men: OR = 0.8 (0.5–1.2) Women: OR = 0.5 (0.3–0.9) Colon: OR = 0.9 (0.9–1.1) Rectum: OR = 0.8 (0.7–0.9)	Matched on age, sex, residence, and urban/rural status Adjusted for age, sex, rural/urban status, education, first-degree family CRC history, BMI, and intake of total energy and red meat
Aune et al., 2009 [45] Montevideo (Uruguay)	1996–2004	Hospital Cases: 3539 Controls: 2032	Both 26–89 years	Personal interview: FFQ with 64 food items a yr before disease diagnosis	Grain legumes (kidney beans and lentils) Legume: Median 14.38 vs. 1.35 g/d OR = 0.43 (0.32–0.59) Beans: Median 9.44 vs. 0 g/d OR = 0.44 (0.31–0.61) Lentils: Median 11.68 vs. 0 g/d OR = 0.53 (0.38–0.75)	Matching not specified Adjusted for age, sex, residence, BMI, education, income, interviewer, smoking status and history, alcohol consumption, mate drinking status, and intake of total energy, dairy products, fatty foods (eggs, cake,

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Reference, region (country)	Study period	Study design, no. controls/cases	Sex, age	Diet assessment	Grain legume, quantity for comparison, risk estimates (95% CI)	Matching/adjusting for confounders
						custard, butter), fruits and vegetables, and total meat
Abu Mweis et al., 2015 [43] (Jordan)	2010–2012	Hospital Cases: 167 Controls: 240	Both >18 years	Self-administered FFQ with 109 food and beverage items (DHQ 1) a yr before disease diagnosis	Lentils >1× vs. <1×/wk OR = 1.49 (0.80–2.79)	Matched by age, sex, occupation, and marital status Adjusted for age, sex, family CRC history, physical activity, smoking, education level, marital status, work, income, and total energy intake
Tayyem et al., 2015 [44] (Jordan)	2010–2012	Hospital Cases: 220 Controls: 281	Both >18 years	Self-administered FFQ with 109 food and beverage items (DHQ 1) a yr before disease diagnosis	Lentils 1×/wk vs. <1×/mo OR = 1.3 (0.72–2.4) White beans 1×/wk vs. <1×/mo OR = 0.86 (0.37–2.1) Green beans 1×/wk vs. <1×/mo OR = 1.0 (0.57–2.2) Peas 1×/wk vs. <1×/mo OR = 1.0 (0.44–2.0)	Matched by age, sex, occupation, and marital status Adjusted for age, sex, family CRC history, physical activity, smoking, education level, marital status, work, income, and total energy intake

*Statistically significant association of legume consumption and colorectal neoplasia.
CRA: colorectal adenoma; CRC: colorectal cancer; FFQ: food frequency questionnaire; IBD: inflammatory bowel disease; mo: month; N/A: not available; OR: odds ratio; RR: relative risk; wk: week; 95% CI: 95% confidence interval.
1 serving of legume equals 0.5 cup of cooked legumes (~90 g) [7].

Table 1. Description of retrospective case-control studies of grain legume consumption and colorectal neoplasia.

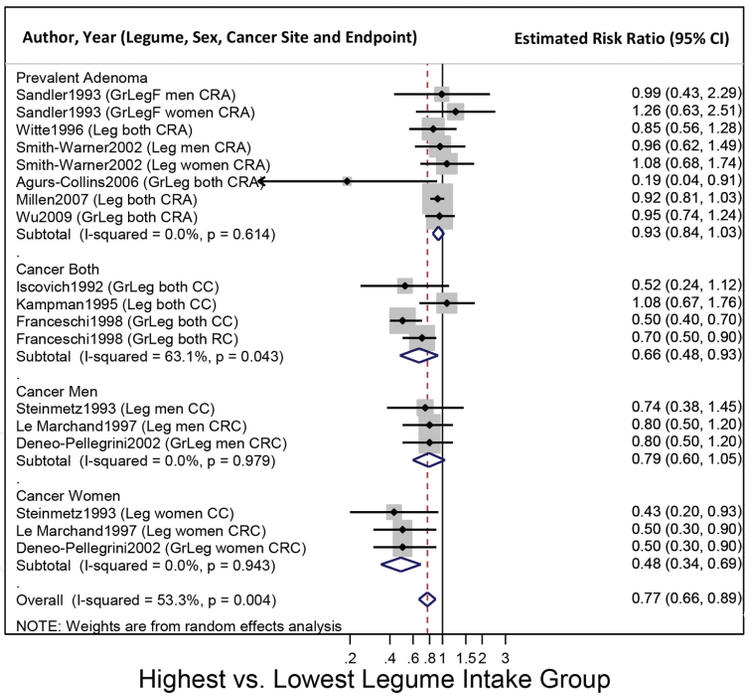

Figure 1. Forest plot of legume consumption (highest vs. lowest category) and colorectal neoplasia risk in retrospective studies stratified by type of neoplastic lesion and gender (only for cancer studies). The dot in each study indicates the estimated risk ratio, vertical bars represent 95% CI, and the size of gray square box reflects the study's weight in the random effects meta-analysis. The straight line indicates no association and the dashed line indicates the summary risk estimate across all studies. The open diamond on the bottom indicates the pooled risk estimate and the right vertices of the diamond reflect the 95% CI. CC: colon cancer; RC: rectal cancer; CRC: colorectal cancer; CRA: colorectal adenoma; GrLeg: grain legume; GrLegF: grain legume fiber; Leg: legume; LegF: legume fiber.

Meta-analysis using a random effects model of natural log odds ratios (OR) in STATA was possible for 12 case-control studies [46–52, 55–57, 59, 60] that included 12,408 cases and 42,473 controls. We had to exclude the four oldest case-control studies [42, 53, 54, 58] because the 95% CIs were not reported and two case-control studies [43, 44] provided only estimates of individual grain legumes. We checked for heterogeneity of estimates, influential risk estimates, and publication bias using funnel plots and Egger's method. When comparing the highest versus the lowest legume intake group, we observed a protective effect of legume consumption on CRA (relative risk (RR) = 0.93; 95% CI: 0.84–1.03; $P = 0.15$) and CRC (RR = 0.65; 95% CI: 0.54–0.77; $P < 0.001$). There was moderate heterogeneity (30.2%) among studies for CRC risk ($P = 0.17$), but <0.01% for CRA risk. The range of risk estimates was 0.56–0.65 for CRC after removing one study at a time. No significant publication bias was observed ($P = 0.11$). The heterogeneity among CRC risk estimates could be explained by gender-specific differential dietary recalls (**Figure 1**); the protective effect of legume consumption on CRA was in men, RR = 0.79 (95% CI: 0.84–1.03; $P = 0.10$; <0.01 heterogeneity), in women, RR = 0.49 (95% CI: 0.34–0.69; $P < 0.0001$; <0.01% heterogeneity), and intermediate RR = 0.67 (95% CI: 0.48–0.93; $P = 0.02$; 63.1% heterogeneity) in studies that did not provide gender-specific estimates.

In prospective cohort studies, dietary information of cohorts or groups of healthy individuals at the time of study recruitment is linked to subsequent disease outcomes. We evaluated the relation between legume consumption and colorectal neoplasia in 15 peer-reviewed publications from 11 prospective cohorts (1,621,519 participants with 13,546 cases), 11 reported cancer as endpoint [61–71] and the remaining four studies reported incident and/or prevalent adenomas as endpoint [72–75] (**Table 2**). All, except for two European cohorts, were U.S. cohorts. Risk estimates were reported for men in six and for women in eight prospective cohorts. Risk estimates specific to colon and rectum were reported in two and one cohorts, respectively. Risk estimates specific to the intake of legumes, legume fiber, grain legumes, and grain legume fiber were reported in three, three, three, and two cohorts, respectively. Two cohorts (Adventist Health Study and Polyp Prevention Trial) showed significant protective effects of grain legume consumption [69, 72, 75]. Four cohorts (Breast Cancer Detection Demonstration Project, Women's Health Study, Multiethnic Cohort Study, and NIH-AARP Study) showed a protective effect on CRC risk, the effect was statistically significant in some statistical models in the latter three cohorts [63, 64, 66–68]. Two cohorts (Nurses' Health Study and Health Professionals' Follow-up Study) showed a protective effect of legume consumption for CRA only [65, 73, 74]. Only three of the 11 cohorts (Iowa Women's Health Study and two European cohorts) showed no effects of legume consumption on CRC risk [61, 62, 70, 71].

Reference, cohort, country	Follow-up period	Study size, case no.	Sex, age	Diet assessment	Grain legume, quantity for comparison, risk estimates (95% CI)	Adjustment for confounders
Incident colorectal adenoma						
Lanza et al., 2006 [72]	1991–1994; 4-yr trial;	1905, 629	Both, >35 years	Four annual self-	Grain legumes (dry beans and lentils)	Adjusted for age, NSAIDs, sex,

Reference, cohort, country	Follow-up period	Study size, case no.	Sex, age	Diet assessment	Grain legume, quantity for comparison, risk estimates (95% CI)	Adjustment for confounders
U.S., Polyp Prevention Trial (PPT)	incident CRA <3 yrs old	No CRC, IBD history		administered FFQ with 27 food items and one grain legume question for previous yr	Mean: 45.1 vs. 3.1 g/d Any: OR = 0.78 (0.58–1.04) Men: OR = 0.69 (0.48–0.99) Advanced: OR = 0.30 (0.15–0.60)	intervention group, and sex by intervention group
Michels et al., 2006 [73] U.S., Nurses' Health Study (NHS)	Diet: 1980–1994, incident CRA >2 yrs old	9735, 633 No CRA, IBD history	Women 30–55 years in 1976	Self-administered FFQ with 61 food items for previous yr	Legumes (beans, lentils, peas, lima beans, tofu, soybeans) ≥5 vs. ≤ 1 serving/wk New Incidence only: OR = 0.67 (0.51–0.90) Trend: OR = 0.92 (0.87–0.98)	Adjusted for age, family CRC history, height, BMI, regular vigorous exercise, regular aspirin use, pack-years of smoking, current multivitamin supplement use, alcohol consumption, menopausal status, postmenopausal hormone use, and intake of total energy, red meat, and calcium
Tantamango et al., 2011 [75] U.S., Adventist Health Study (AHS)	Diet: 1976–1977, Endpoint: 2002–2004 incident CRA <20 yrs old	2818, 441 No CRC, IBD history	Both, All underwent colonoscopy, no age exclusion	Self-administered FFQ with 55 food and beverage items	Grain legumes (beans, lentils, split peas) ≥3×/wk vs. <1×/mo OR = 0.67 (0.44–1.01) Trend: $P = 0.02$	Adjusted for age, sex, education, BMI, and red meat intake
Prevalent colorectal adenoma						
Platz et al., 1997 [74] U.S., Health and Professionals' Follow-up Study (HPFS)	1986–1994	16,448, 690 No CRA, IBD history	Men 40–75 years All underwent colonoscopy	Self-administered FFQ with 127 food items for previous yr	Legume fiber (beans, lentils, peas, lima beans, tofu, soybeans) Median 2.6 vs. 0.5 g/d	Adjusted for age, family CRC history, prior endoscopy, BMI, smoking, multivitamin use, physical activity,

Reference, cohort, country	Follow-up period	Study size, case no.	Sex, age	Diet assessment	Grain legume, quantity for comparison, risk estimates (95% CI)	Adjustment for confounders
					RR = 0.82 (0.60–1.11) Trend: *P* = 0.06	regular aspirin use, and intake of energy, alcohol, red meat, folate, and methionine
Michels et al., 2006 [73] U.S., Nurses' Health Study (NHS)	Diet: 1980–1994 Endpoint: 1980–1998	34,467, 1720 No CRC and IBD history	Women 30–55 years in 1976	Self-administered FFQ with 61 food items for previous yr	Legumes (beans, lentils, peas, lima beans, tofu, soybeans) ≥5 vs. ≤1 serving/wk OR = 0.89 (0.75–1.05) Trend: OR = 0.96 (0.93–1.00)	Adjusted for age, family CRC history, height, BMI, regular vigorous exercise, regular aspirin use, pack-years of smoking, current multivitamin supplement use, alcohol consumption, menopausal status, postmenopausal hormone use, and intake of total energy, red meat, and calcium
Colon cancer						
Steinmetz et al., 1994 [70] U.S., Iowa Women's Health Study (IWHS)	1986–1990	41,837, 212	Women, 55–69 years at baseline, no CRC history	Self-administered FFQ with 127 food items for previous yr	Legumes (beans, lentils, peas, lima beans, tofu, soybeans) ≥1.0 vs. 0 servings/wk RR = 0.95 (0.66–1.36)	Adjust for age and total energy intake
Singh and Fraser, 1998 [69] U.S., Adventist Health Study (AHS)	1976–1982	32,051 157 Non-hispanic white	Both >25 years	Self-administered FFQ with 55 food items	Grain legumes (beans, lentils, split peas) >2× vs. <1×/wk RR = 0.53 (0.33–0.86)	Adjusted for age, sex, BMI, physical activity, parental CRC history, smoking, alcohol consumption, and aspirin use

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Reference, cohort, country	Follow-up period	Study size, case no.	Sex, age	Diet assessment	Grain legume, quantity for comparison, risk estimates (95% CI)	Adjustment for confounders
Colorectal cancer						
Michels et al., 2000 [65] U.S., Nurses' Health Study (NHS)	1980–1996	88,764, 724	Women 30–55 years	Self-administered FFQ with 127 food items for previous yr	Legumes (beans, lentils, peas, lima beans, tofu, soybeans) ≥4 vs. <1 serving/wk RR = 1.26 95% CI N/A RR = 1.49 (1.04–2.12) per additional serving/wk	Adjusted for age, family CRC history, sigmoidoscopy, height, BMI, pack-years of smoking, alcohol consumption, physical activity, intake of total energy and red meat, and use of menopausal hormones, aspirin, and vitamin supplements
Michels et al., 2000 [65] U.S., Health and Professionals' Follow-up Study (HPFS)	1986–1996	47,325, 457	Men 40–75 years	Self-administered FFQ with 127 food items for previous yr	Legumes (beans, lentils, peas, lima beans, tofu, soybeans) ≥4 vs. <1 serving/wk RR = 0.97 95% CI N/A RR = 0.90 (0.57–1.42) per additional serving/wk	Adjusted for age, family CRC history, sigmoidoscopy, height, BMI, pack-years of smoking, alcohol consumption, physical activity, intake of total energy and red meat, and use of menopausal hormones, aspirin, and vitamin supplements
Voorrips et al., 2000 [71] Netherlands Cohort Study on Diet and Cancer (NCSDC)	1986–1992	Male: 58,279, 514 Women: 62,573, 396	Both, 55–69 years	Self-administered FFQ with 155 food items for previous yr	Grain legumes (green and lima beans) Male: Median 62 vs. 11 g/d Colon RR = 1.13 (0.77, 1.64) Rectum: RR = 0.92 (0.58–1.47) Female: Median 58 vs. 11 g/d	Adjusted for age, alcohol consumption, and family CRC history

Reference, cohort, country	Follow-up period	Study size, case no.	Sex, age	Diet assessment	Grain legume, quantity for comparison, risk estimates (95% CI)	Adjustment for confounders
					Colon RR = 0.79 (0.52, 1.20) Rectum: RR = 1.01 (0.53–1.94)	
Mai et al., 2003 [64] U.S., Breast Cancer Detection Demonstration Project (BCDDP)	1987–1998	45,491, 487	Women Age range N/A	Self-administered FFQ with 62 food items for previous yr	Grain legume fiber >1.38 vs. <0.20 g/1000 kcal/d RR = 0.84 (0.63–1.10)	Unadjusted
Bingham et al., 2003 [61] 10 EU countries, EPIC	1992–2002	519,978, 1065	Both, 35–70 years	Country-specific FFQ with 300–350 food items	Legume fiber Mean: 1.73 vs. 0.45 g/d HR = 1.04 (0.84–1.30)	Adjusted for age, weight, height, sex, intake of nonfat and fat energy, and stratified by center
Bingham et al., 2005 [62] 10 EU countries, EPIC	1992–2004	519,978, 1721	Both, 35–70 years	Country-specific FFQ with 300–350 food items	Legume fiber Mean: 1.9/1.0 vs. 0 g/d HR = 0.94 (0.79–1.14)	Adjusted for age, weight, height, sex, intake of nonfat and fat energy, and stratified by center
Lin et al., 2005 [63] U.S., Women's Health Study (WHS)	1993–2003	39,876, 223	Women ≥45 years	Self-administered FFQ with 131 food items for previous yr	Legumes (dry beans, lentils, peas, lima and green beans, tofu, soybeans) Median 0.9 vs. 0.1 serving/d RR = 0.83 (0.54–1.28) Legume fiber Median 1.8 vs. 0.4 g/d RR = 0.60 (0.40–0.91)	Adjusted for age, randomized treatment assignment, BMI, first-degree CRC family history, colon polyp history, physical activity, smoking status, baseline use of aspirin, hormone replacements, menopausal status, alcohol consumption, and intake of total energy and red meat
Nomura et al., 2007 [66] U.S., Multiethnic	1993–2001	191,011, 2110	Both, 45–75 years	Self-administered	Legume fiber	Adjusted by age, ethnicity, time since

Reference, cohort, country	Follow-up period	Study size, case no.	Sex, age	Diet assessment	Grain legume, quantity for comparison, risk estimates (95% CI)	Adjustment for confounders
Cohort Study (MEC)				FFQ with 180 food items	Men: Median 7.6 vs. 0.3 g/1000 kcal/d CRC: RR = 0.81 (0.65–1.01) P_{trend} = 0.04 Women: Median 5.8 vs. 0.2 g/1000 kcal/d CRC: RR = 1.02 (0.82–1.27)	cohort entry, and age at cohort
Park et al., 2007 [67] U.S., NIH–AARP Diet and Health Study	1995–2000	488,043, 2972	Both, 50–71 years at baseline	Self-administered FFQ with 124 food items for previous yr	Grain legumes (dried beans, green beans, and peas) Men: Median 0.69 vs. 0.08 servings/d RR = 0.95 (0.83–1.09) Significant for age adjusted RR = 0.85 (0.74–0.97) Women: Median 0.81 vs. 0.09 servings/d RR = 1.13 (0.91–1.40)	Adjusted for education, physical activity, smoking, alcohol consumption, and intake of total energy, red meat, and calcium
Schatzkin et al., 2007 [68] U.S., NIH–AARP Diet and Health Study	1995–2000	489,611, 2974	Both, 50–71 years at baseline	Self-administered FFQ with 124 food items for previous yr	Grain legume fiber Median 2.3 vs. 0.2 g/1000 kcal/d RR = 0.93 (0.83–1.04) Significant for age-and sex-adjusted RR = 0.89 (0.79–0.99)	Adjusted for sex, physical activity, smoking, menopausal hormone therapy, and intake of total energy, red meat, calcium, and folate

*Statistically significant association of legume consumption and colorectal neoplasia.
CRC: colorectal cancer; CRA: colorectal adenoma; FFF: food frequency questionnaire; HR: hazard ratio; IBD: inflammatory bowel disease; N/A: not available; OR: odds ratio; RR: relative risk; 95% CI: 95% confidence interval.
1 serving of legume equals 0.5 cup of cooked legumes (~90 g) [7].

Table 2. Prospective cohort studies of grain legume consumption and colorectal neoplasia.

For the meta-analysis, we had to exclude the CRC risk estimates of two cohorts because the risk estimates did not include 95% CI [65], leaving us with 1,533,527 participants including 12,408 cases. When comparing the highest versus the lowest legume intake group, we observed, as shown in **Figure 2**, a protective effect of grain legume consumption on colorectal neoplasia (RR = 0.89; 95% CI: 0.59–0.88; $P = 0.001$). The protective effect attenuated from incident CRA (RR = 0.72; 95% CI: 0.60–0.87; $P < 0.001$) over prevalent CRA (RR = 0.87; 95% CI: 0.75–1.01; $P = 0.07$) to CRC (RR = 0.93; 95% CI: 0.86–1.01; $P = 0.08$). There was little heterogeneity (18.3%) among studies, which was further decreased after stratifying for neoplastic endpoint (**Figure 2**). No significant publication bias was observed ($P = 0.13$). We observed a nonlinear relationship between legume consumption and colorectal neoplasia, as the protective effect of legume consumption for incident CRA (**Table 2**) was limited to the highest legume intake group, which corresponds to daily consumption of at least 0.5 servings of legumes (~45 g/d). In comparison, the 2015 U.S. dietary guidelines recommend three servings/wk (~39 g/d), which is lower than six servings/wk of the 2005 guidelines [7, 76].

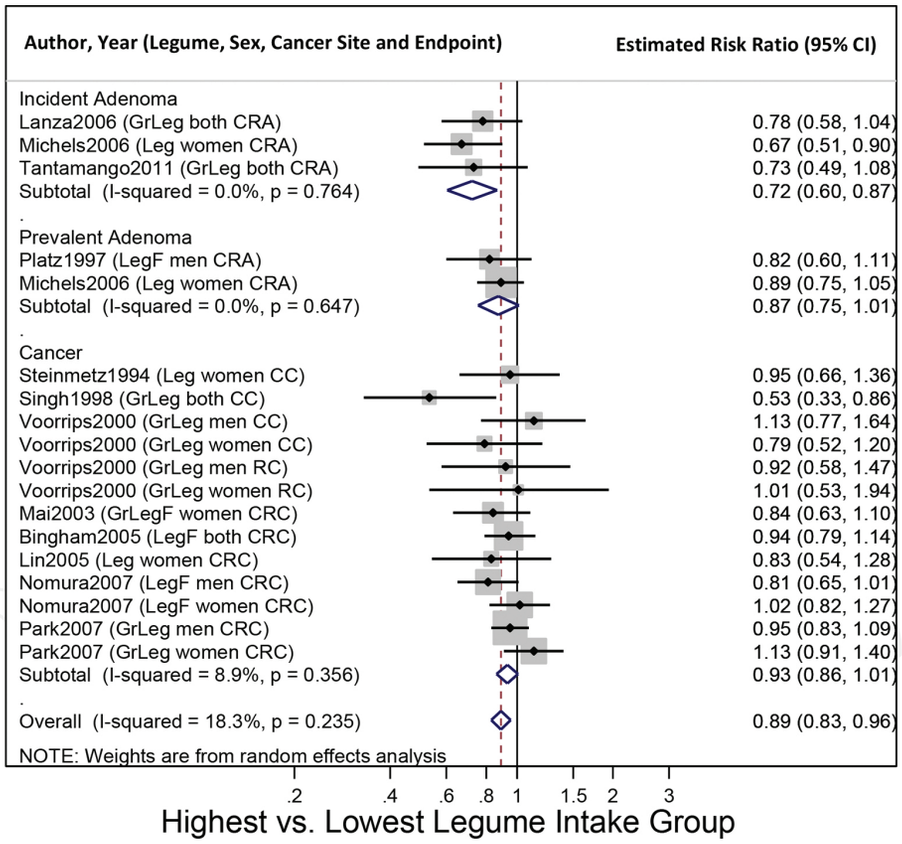

Figure 2. Forest plot of legume consumption (highest vs. lowest category) and colorectal neoplasia risk in prospective studies stratified by type of neoplastic lesion. The dot in each study indicates the estimated risk ratio, vertical bars represent the 95% CI and the size of gray square box reflects the study's weight in the random effects Meta-analysis studies. The straight line indicates no association and the dashed line indicates the summary risk estimate across all studies. The open diamond on the bottom indicates the pooled risk estimate and the right vertices of the diamond reflect the 95% CI. CC: colon cancer; RC: rectal cancer; CRC: colorectal cancer; CRA: colorectal adenoma; GrLeg: grain legume; GrLegF: grain legume fiber; Leg: legume; LegF: legume fiber.

Our risk estimates (**Table 3**) are similar to those obtained previously from meta-analyses between legume consumption (including soybeans) and CRA (RR = 0.73; 95% CI: 0.61–0.88) and CRC (RR = 0.91; 95% CI: 0.84–0.98) [14, 15], as well as legume fiber consumption and CRC (RR = 0.89; 95% CI: 0.78–1.02) [16]. Thus, we conclude that there is limited evidence suggesting that daily grain legume consumption decreases CRC risk in humans, all of which are based on observational studies. This is consistent with what has been previously concluded for the evidence on the relation between stomach or prostate cancer risk and legume consumption [34].

Factor	Studies	Pooled risk ratio		Heterogeneity		Eggers	References
	(estimates)	RR (95% CI)	*P*	I^2 (%)	*P*	*P*	
Overall	23 (36)	0.84 (0.78–0.90)	0.005	41.9	<0.001	0.02	[46–52, 55–57, 59, 60, 62–64, 66, 67, 69–75]
Endpoint							
Incident adenoma	3 (3)	0.72 (0.60–0.87)	<0.001	0	0.76	0.90	[72, 73, 75]
Prevalent adenoma	8 (10)	0.91 (0.84–0.99)	0.03	0	0.73	0.60	[47–52, 73, 74]
Cancer	14 (23)	0.82 (0.74–0.91)	<0.001	54.4	0.001	0.02	[46, 55–57, 59, 60, 62–64, 66, 67, 69–71]
Study type							
Retrospective	12 (18)	0.77 (0.66–0.89)	<0.001	53.3	0.004	0.11	[46–52, 55–57, 59, 60]
Prospective	11 (18)	0.89 (0.83–0.96)	0.001	18.3	0.24	0.13	[62–64, 66, 67, 69–75]
Gender							
Men	10 (11)	0.89 (0.81–0.97)	0.009	0	0.80	0.40	[46, 47, 49, 59, 60, 66, 67, 71, 72, 74]
Women	11 (13)	0.86 (0.75–0.98)	0.03	50.7	0.02	0.14	[46, 47, 49, 59, 60, 64, 66, 67, 70, 71]
Legume type							
Legume	13 (17)	0.88 (0.82–0.94)	<0.001	4.5	0.40	0.10	[48, 49, 51, 57, 59, 60, 62, 63, 66, 70, 73, 74]
Grain legume	11 (19)	0.80 (0.71–0.92)	0.001	58.1	0.001	0.09	[46, 47, 50, 52, 55, 56, 64, 67, 69, 71, 72, 75]
Legume part							
Grain	18 (29)	0.82 (0.74–0.89)	<0.001	49.6	0.001	0.01	[46, 48–52, 55–57, 59, 60, 63, 67, 69–73, 75]
Fiber	6 (8)	0.92 (0.85–0.99)	0.02	0	0.78	0.92	[47, 62, 64, 66, 68, 74]

Factor	Studies	Pooled risk ratio		Heterogeneity		Eggers	References
	(estimates)	RR (95% CI)	*P*	I^2 (%)	*P*	*P*	
Cancer site							
Colon	8 (10)	0.69 (0.54–0.88)	0.003	63.6	0.003	0.94	[45, 55–57, 60, 69–71]
Rectum	3 (4)	0.70 (0.49–1.00)	0.05	63.9	0.04	0.69	[45, 55, 71]
Continent/country							
Europe	4 (8)	0.83 (0.67–1.03)	0.09	64.9	0.006	0.77	[55, 57, 62, 71]
USA	16 (23)	0.88 (0.82–0.94)	<0.001	24.5	0.14	0.04	[47–52, 59, 63, 64, 66, 67, 69, 70, 72–75]

Pooled risk estimates with 95% confidence intervals in parentheses compare risk of developing colorectal cancer/adenoma of the highest versus the lowest grain legumes intake group. Study number will not add up to overall number because for overall study we used most combined risk estimates available. Eggers *P*-value indicates probability for publication bias.

Table 3. Higher grain legume consumption decreases risk of colorectal tumorigenesis: meta-analysis of 23 human studies.

The next step needs to be a long-term intervention study of daily grain legume consumption in a high CRC risk cohort. Dietary compliance will be a major challenge in Western countries because <10% of the population consumes grain legumes on a daily basis [6, 10, 11]. Moreover, it is much easier to take a daily supplement or a medication than consuming a chemo-preventive diet. At the same time, it is unrealistic to expect a chemo-preventive effect of a food, supplement, or medication when it is sporadically consumed. We previously identified markers of dietary compliance for grain legume consumption in human and animal studies [77], which allows for compliance monitoring. Intention-to-treat analysis, the gold standard for statistical evaluation of intervention studies, assumes high compliance. Statistical methods that account for dietary exposure markers and low compliance are needed when evaluating the evidence from dietary intervention studies.

4. Grain legumes and colorectal neoplasia in animal studies

As shown in **Table 4**, 14 animal studies evaluated the effect of grain legume consumption on colorectal tumorigenesis using 253 animals (248 males and five females) on control diets and 355 animals (350 males and five females) on 19 different grain-legume-containing diets [78–89]. Eight diets contained whole dry beans, seven contained dry bean fractions (three fiber factions, three ethanol extract, and one ethanol extract residue); two diets each contained lentils or chickpeas, and one diet each contained black-eyed peas or dry peas. In three studies, the animals were intragastrically tubed with dry beans and/or dry bean fiber [85, 87], whereas in the remaining 11 studies grain legumes or their fractions were included in the diet. Ten studies were conducted with rats and four with mice. All but one study [79] used azoxymethane

(AOM), which is commonly used in animal models of human CRC to induce DNA mutations by alkylating DNA primarily at the O^6-guanidine residues [90, 91]. After AOM induction, we promoted tumor formation in two unpublished studies with the colon irritant dextran sodium sulfate (DSS); this is an established inflammation-associated animal model of human CRC [92]. Bean treatment started before tumor induction in nine studies, after tumor induction in three, and after tumor induction and promotion in two studies. Study endpoints were ACF in seven studies, adenomas and adenocarcinomas in five, and tumors in two studies.

Reference	Animal	Diet, animals/diet	Experimental design	Tumor endpoints
Colorectal tumors:				
Hughes et al., 1997 [78]	F344 male rats	Control: casein diet, *n* = 20 Treatment: Pinto beans (59% of diet) *n* = 21	2× AOM (15 mg/kg BW) a wk apart First AOM: 6 wk of age Diet Start: 1 wk after last AOM Study End: 34 wk after last AOM	Colon adenomas, adenocarcinomas (incidence and multiplicity)
McIntosh et al., 1998 [79]	Sprague-Dawley male rats	Control: modified AIN-1976, *n* = 18 Treatment: Chickpeas (45% of diet) *n* = 18	3× DMH (15 mg/kg BW) a wk apart First DMH: 9 wk of age Diet start: 4 wk before first DMH Study End: 22 wk after last DMH	Colon adenomas + adenocarcinomas (incidence and multiplicity)
Hangen & Bennink, 2002 [80]	F344 male rats	Control: modified AIN-93G, *n* = 28 Treatments: Black beans (75% of diet) *n* = 32 Navy beans (75% of diet) *n* = 28	2× AOM (15 mg/kg BW) a wk apart First AOM: 7 wk of age Diet Start: 4 wk before first AOM Study End: 31 wk after last AOM	Colon adenomas, adenocarcinomas (incidence and multiplicity)
Bobe et al., 2008 [81]	Ob/Ob male mice	Control: modified AIN-93G, *n* = 40 Treatments: Navy beans (74% of diet) *n* = 34 Navy bean ethanol residue (74% of diet) *n* = 38 Navy bean ethanol extract (9% of diet) n=39	2× AOM (7 mg/kg BW) a wk apart First AOM: 7 wk of age Diet Start: 1 wk after last AOM Study End: 27 wk after last AOM	Colon adenomas, adenocarcinomas, tumors (incidence and multiplicity)

Reference	Animal	Diet, animals/diet	Experimental design	Tumor endpoints
Rondini & Bennink, 2012 [82]	F344 male rats	Control: modified AIN-93G, *n* = 25 Treatment: Black beans (74% of diet) *n* = 25	2× AOM (15 mg/kg BW) a wk apart First AOM: 4 wk of age Diet Start: 1 wk after last AOM Study End: 31 wk after last AOM	Colon adenomas + adenocarcinomas incidence
Bobe et al. (unpublished)	FVB/N male mice	Control: AIN-93G, *n* = 32 Treatment: Navy bean ethanol extract (10% of diet) *n* = 33	AOM (10 mg/kg BW) 6 wk of age DSS (2% drinking water) 1 week starting 1 wk after DSS Diet Start: 10 days after AOM Study End: 102 days after AOM	Colorectal tumor multiplicity
Bobe et al. (unpublished)	FVB/N male mice	Control: AIN-93G, *n* = 20 Treatment: Navy bean ethanol extract (10% of diet) *n* = 20	AOM (10 mg/kg BW) 6 wk of age DSS (2% drinking water) 1 week starting 1 wk after DSS Diet Start: 10 days after AOM Study End: 53 days after AOM	Colorectal tumor multiplicity
Colon aberrant crypt foci (ACF):				
Rijken et al., 1999 [83]	Sprague-Dawley male rats	Control: AIN-93M, *n* = 15 Treatment: Dry peas (5.9% of diet) *n* = 15	2× AOM (15 mg/kg BW) 3 d apart First AOM: 10 wk of age Diet Start: 2 wk before first AOM Study End: 11 wk after last AOM	Colon aberrant crypt foci (total, multiplicity)
Murillo et al., 2004 [84]	CF-1 female mice	Control: Harland Teklad 4% Diet 7001, *n* = 5 Treatment: Chickpea flour (10% of diet) *n* = 5	2× AOM (10 mg/kg BW) a wk apart First AOM: 5 wk of age Diet Start: 2 wk before first AOM Study End: 7 wk after last AOM	Control: 1.13 ACF/cm^2 colon 0 >4 foci ACF Chickpea: 0.41 ACF/cm^2 colon 2.2 ± 0.37 >4 foci ACF
Boateng et al., 2007 [89]	F344 male rats	Control: AIN-93G, *n* = 8 Treatments: Pinto beans (20% of diet) *n* = 8	2× AOM (15 mg/kg BW) a wk apart First AOM: 7 wk of age Diet Start: 3 wk before	Control: 183 ± 23 ACF Pinto: 64 ± 8 ACF Peas: 40 ± 4 ACF

Reference	Animal	Diet, animals/diet	Experimental design	Tumor endpoints
		Black-eyed peas (20% of diet) $n = 8$	first AOM Study End: 9 wk after last AOM	
Feregrino-Perez et al., 2008 [85]	Sprague-Dawley male rats	Control:2018S Harland Teklad $n = 10$ Treatments: Daily intragastric tubing Dry bean Negro 8025 (3.2 g/kg BW) $n = 10$ Dry bean Negro 8025 fiber fraction (1.84 g/kg BW) $n = 10$	2× AOM (15 mg/kg BW) a wk apart First AOM: 5 wk of age Diet Start: 1 wk before first AOM Study End: 5 wk after last AOM	Distal colon zone: Control: 4.2 ± 0.6 ACF Dry bean: 2.2 ± 0.6 ACF Fiber fraction: 2.0 ± 0.8 ACF Using DAPI stain
Faris et al., 2009 [86]	F344 male rats	Control: AIN-93G, $n = 10$ Treatments: Whole lentils (5% of diet) $n = 10$ Split lentils (5% of diet) $n = 9$	2× AOM (15 mg/kg BW) a wk apart First AOM: 10 wk of age Diet Start: 5 wk before first AOM Study End: 17 wk after last AOM	Control: 178 ± 24 ACF 12.0 ± 1.04 >3 foci ACF Dry bean: 70 ± 8 ACF 2.66 ± 0.09 >3 foci ACF Fiber fraction: 94 ± 17 ACF 5.56 ± 1.05 >3 foci ACF
Vergara-Castaneda et al., 2010 [87]	Sprague-Dawley rats male	Control:2018S Harland Teklad $n = 12$ Treatments: Daily intragastric tubing Dry bean Bayo Madero (5.7 g/kg BW) $n = 12$ Dry bean Bayo Madero fiber fraction (2.5 g/kg BW) $n = 10$	2× AOM (15 mg/kg BW) a wk apart First AOM: 6 wk of age Diet Start: 1 wk before first AOM Study End: 7 wk after last AOM	Distal colon zone: Control: 6.6 ± 0.40 ACF Dry bean: 0.8 ± 0.20ACF Fiber fraction: 1.5 ± 0.72 ACF
Feregrino-Perez et al., 2014 [88]	Sprague-Dawley male rats	Control:2018S Harland Teklad $n = 10$ Treatments: Daily intragastric tubing Dry bean Negro 8025 fiber fraction (1.84 g/kg BW) $n = 10$	2× AOM (15 mg/kg BW) a wk apart First AOM: 5 wk of age Diet Start: 1 wk before first AOM Study End: 5 wk after last AOM	Distal colon zone: Control: 21.0 ± 3.25 ACF Fiber fraction: 7.20 ± 2.95 ACF

AOM: azoxymethane; BW: body weight; DMH: dimethylhydrazine; DSS: dextran sodium sulfate. ACF were measured using methylene blue staining unless otherwise noted.

Table 4. Experimental design and endpoints in animal studies of grain legume intake and colorectal tumorigenesis.

Table 5 shows individual and pooled risk estimates of the seven studies with tumor endpoints. For calculating risk estimates of tumor and ACF multiplicity, we calculated standardized mean differences and variation from reported means and standard errors. Grain legume consumption inhibited colorectal tumorigenesis. The protective effect of dry bean consumption attenuated with progressive tumor stage from tumor incidence (OR = 0.21; 95% CI: 0.11–0.43) over combined adenoma and adenocarcinoma incidence (OR = 0.32; 95% CI: 0.17–0.60) to adenocarcinoma incidence (OR = 0.38; 95% CI: 0.20–0.74). Similarly, the protective effect of grain legume consumption attenuated from ACF multiplicity (OR = 0.07; 95% CI: 0.03–0.14 with stronger effect on larger ACFs; **Table 4**) over tumor multiplicity (OR = 0.24; 95% CI: 0.16–0.36) to combined adenoma and adenocarcinoma multiplicity (OR = 0.52; 95% CI: 0.31–0.89) and adenocarcinoma multiplicity (OR = 0.52; 95% CI: 0.27–0.98; $P = 0.04$). Given that the chemopreventive effect of legumes was reported when grain legumes were fed before as well as after tumor induction and/or tumor promotion, we conclude that grain legumes inhibit colorectal tumorigenesis at different tumor stages.

Reference,	Legume	Adenocarcinoma		Adenoma + adenocarcinoma		Tumor	
Year		Incidence	Multiplicity	Incidence	Multiplicity	Incidence	Multiplicity
Hughes1997	PintoBW	0.38 (0.10–1.45)	0.19 (0.06–0.60)	0.31 (0.08–1.19)	0.20 (0.06–0.66)		
Hangen2002	BlackBW	0.19 (0.05–0.77)		0.25 (0.09–0.75)			
Bennink2012	BlackBW			0.15 (0.04–0.52)			
Hangen2002	NavyBW	0.30 (0.08–1.11)		0.22 (0.07–0.68)			
Bobe2008	NavyBW	1.55 (0.38–6.31)	1.11 (0.48–2.55)	0.59 (0.18–1.98)	0.90 (0.39–2.07)	0.32 (0.11–0.95)	0.29 (0.12–0.68)
Bobe2008	NavyBER	0.24 (0.03–2.28)	0.56 (0.25–1.26)	0.23 (0.07–0.71)	0.61 (0.27–1.36)	0.23 (0.07–0.71)	0.22 (0.09–0.51)
Bobe2008	NavyBEE	0.23 (0.02–2.16)	0.45 (0.20–1.01)	0.09 (0.01–0.74)	0.46 (0.21–1.04)	0.08 (0.02–0.38)	0.17 (0.07–0.39)
BobeUnpubl	NavyBEE						0.20 (0.05–0.74)
BobeUnpubl	NavyBEE						0.34 (0.14–0.85)
McIntosh1998	ChickpeaW			2.50 (0.65–9.65)			
Pooled odds ratio		**0.38 (0.20–0.74)**	**0.52 (0.27–0.98)**	**0.32 (0.17–0.60)**	**0.52 (0.31–0.89)**	**0.21 (0.11–0.43)**	**0.24 (0.16–0.36)**

For multiplicity, odds ratios and their 95% confidence intervals were estimated from reported means and standard errors by calculating standardized mean differences. B: bean; BEE: bean ethanol extract; BER: bean ethanol residue; W: whole beans; multiplicity: number of tumor/animal.
The P-values are in this order from left to right: P=0.004; P = 0.04; P< 0.001; P = 0.02; P< 0.001; P< 0.001

Table 5. Risk estimates with 95% confidence intervals (in parentheses) for colorectal tumors in animal studies.

The animal studies have limitations: first, in four of the seven tumor endpoint studies, grain legumes made up the majority of the diet (45–75%; **Table 4**) [78–80, 82], concentrations that are not relevant for human consumption. However, three studies showed a protective effect of the ethanol extract of navy beans fed at 10% of the diet (**Table 4**); the 2015 U.S. dietary guidelines for legume consumption are equivalent to ~2–5% of the diet [76], concentrations that should be evaluated in future animal studies. Second, none of the reported studies included more than one grain legume dosage (**Table 4**), demonstrating a need for dose-response studies in animal CRC models. Third, only one study examined the chemo-preventive effect of grain legumes other than dry beans at the tumor stage (**Table 4**), indicating a need to evaluate the chemo-preventive effect of other grain legumes at the tumor stage. Fourth, further research is needed to demonstrate a chemo-preventive response in female animals, as all but one study [84] examined the response in male animals. Despite these limitations, there is sufficient evidence to conclude that at least dry bean consumption probably decreases colorectal tumorigenesis in male animal models of human CRC.

5. Chemo-preventive compounds in grain legumes

To elucidate which fractions of grain legumes have chemo-preventive properties against colorectal tumorigenesis, we previously fractionated cooked navy beans using 60% ethanol [81]. Both the ethanol extract and the residue inhibited colorectal tumorigenesis in AOM-induced mice, indicating that both fractions contain chemo-preventive compounds. Several studies conducted by Loarca-Piña's research group demonstrated that the non-digestible fraction of dry beans inhibits colon ACF formation in AOM-induced rats [85, 87].

Grain legumes contain three major carbohydrate classes that inhibited colorectal ACF and tumor formation in animal CRC models: resistant starches (cooked grain legumes contain 0.6–4.2%), soluble fiber including the flatulence-inducing α-galacto-oligosaccharides stachyose, verbascose, and raffinose (cooked grain legumes contain 0–3%), and insoluble fiber (cooked grain legumes contain 15–23%); concentrations of those carbohydrate classes vary considerably based on processing methods [1, 2, 7, 93–97]. Resistant starches can be effective at 5–10% of the diet [7, 98–102]. Soluble fiber can inhibit ACF and tumor formation at 2.5–15% of the diet [103, 104], and insoluble fiber can be effective at 5–15% of the diet [104–107].

Grain legumes contain lipid classes that inhibited colorectal ACF and tumor formation in animal models of CRC. Plant sterols (e.g., β-sitosterol, campesterol, and stigmasterol; 0.13–0.24% of grain legume dry weight) attenuate colorectal tumorigenesis in animal studies (gastric intubation of 10–20 mg β-sitosterol/kg body weight or 0.2% of diet) [108–111]. Saponins (0.1–0.5% of grain legume dry weight) are glycolipids, which inhibit ACF formation at concentrations of 0.01–3% of the diets [112–116]; the lower concentrations are relevant for human diets [117]. Processing can decrease saponin concentrations in grain legumes up to 40% [118]. Besides containing phytosterols and saponins, grain legumes are low in lipids and have a favorable fatty acid composition for chemo-prevention (i.e., low in saturated fatty acids and a low Ω3: Ω6 fatty acid ratio) [3, 119, 120].

Grain legumes contain protein classes that inhibited colorectal ACF and tumor formation in animal models of CRC. Trypsin and chymotrypsin protease inhibitors of the Bowman-Birk family inhibit at dietary concentrations of 0.1–0.5% of the diet or 20 mg/kg of body weight for colorectal ACF and tumor formation [121–125]. Lectins (i.e., agglutinins; 0.1–3.5% of grain legume dry weight), which are glycoproteins that bind to epithelial cells, have been shown to inhibit cancer growth in animal tumor transplant studies and colon cancer cells [126–128]. Grain legumes have significant α-amylase inhibitor activity, which may indirectly decrease CRC risk by increasing microbial butyrate production and decreasing blood glucose and insulin after starch consumption [129]. The importance of Bowman-Birk inhibitors, α-amylase inhibitors, and lectins is debatable because 80–90% is lost and denatured during soaking and cooking, respectively [7, 96, 117].

The mineral and vitamin content of grain legumes may confer chemo-preventive effects against colorectal tumorigenesis. Grain legumes contain high concentrations of folate (83–174 μg/100 g of cooked legumes) and potassium (0.29–0.51% of cooked legumes) and low concentrations of sodium (<0.01% of cooked legumes) [7]. A high ratio of potassium to sodium has been reported to decrease CRC risk, and folate intake is established as a protective nutrient against CRC [130, 131]. Chemo-preventive compounds associated with minerals are phytates (0.1–1.9% of grain legume dry weight), the primary plant storage forms of phosphorus [117]. Processing decreases phytate content up to 50% [97, 132]. Phytates inhibit ACF formation at dietary concentrations of 0.02–2% [133–136]; the lower concentrations are relevant for human diets [137].

Grain legumes are a good dietary source of phenolic compounds (1–10 mg gallic acid equivalents/g legume, which is ~0.1–1.0% of grain legume dry weight) [117, 118, 132, 138, 139], many of which inhibited colorectal ACF and tumor formation in animal models of CRC. The three major phenolic groups with chemo-preventive properties are flavonoids (0–5 mg catechin equivalents/g legume), proanthocyanidins (i.e., condensed tannins; 0.2–12 mg catechin equivalents/g legume), and phenolic acids (0.02–0.1% of cooked legume dry weight) [118, 132, 138, 139]. Flavonols (i.e., kaempferol and quercetin), anthocyanidins, and flavan-3-ols are major flavonoid classes in grain legumes that have been demonstrated by us and others to inhibit colorectal tumor multiplicity at concentrations of 0.05–0.3% of the diet [140–144]. Proanthocyanidins can inhibit ACF formation at concentrations of 0.002–1% of the diet or by gavage [145–147]. Phenolic acids include ferulic acid (~0.003% of grain legume dry weight) that inhibited ACF formation at concentrations of 0.25–1% [148–150] and sinapic acid that inhibited ACF formation at concentrations of 20–80 mg/kg of body weight by gavage [151]. The concentrations of the phyto-estrogen group's isoflavonoids (0.005–0.095 mg/kg grain legume) and lignans (0.018–0.266 mg/kg grain legume) are relatively low in grain legumes [152] and, thus, probably contribute little to the chemo-preventive effect of grain legumes. Processing and cooking of grain legumes result in various losses of phenolic compounds, which decreased not only their antioxidant activities but also their antiproliferative properties against colon cancer cells [118, 132, 139]. Thus, food processing plays an important role for the chemo-preventive role of grain legumes [117, 127].

There is sufficient evidence that grain legumes contain various compounds that can exert chemo-preventive effects against colorectal tumorigenesis in animal models of CRC at concentrations that are relevant for human diets. One has to consider that several of the aforementioned compounds are developed by plants as defense mechanisms against herbivores and are at sufficiently high concentrations to be toxic. It has to be noted that most of the aforementioned compounds do not show a consistent chemo-preventive effect in animal models of CRC; further investigation is necessary to elucidate factors, including food processing, that affect the response. Further studies are also warranted to examine whether the effect of the chemo-preventive compounds differs when they are consumed alone or in combination.

6. Molecular mechanisms by which grain legumes inhibit colorectal tumorigenesis

Given the complex mixture of chemo-preventive compounds in grain legumes, it comes to no surprise that grain legumes inhibit hallmarks of cancer [153, 154] at multiple stages of the colorectal tumorigenesis process. (A) Grain legumes can inhibit tumor induction (i.e., the transition from normal to initiated colorectal epithelial cells). First, grain legumes can alter the metabolism of carcinogens (i.e., increased degradation) and pre-carcinogens (i.e., decreased activation). This is accomplished directly by activating the expression of cytochrome P450 and UDP-glucuronosyltransferase (UGT) protein-encoding genes in the liver and indirectly by altering microbiome metabolism of carcinogens (e.g., decreased β-glucuronidase activity) in the colon [87, 155]. Second, grain legumes can act as antioxidants and induce genes involved in the detection and repair of mutated genes [156, 157]. Third, grain legumes may prevent the exposure of colorectal epithelial cells to carcinogens in food and bile by (a) binding carcinogens with non-digestible grain legume compounds [87, 158] and by (b) increasing mucin production of colorectal epithelial cells [159]. Fourth, grain legumes can decrease the colon pH [80] and promote the growth of probiotic bacteria [160] and thereby inhibit the growth of genotoxic bacteria [161, 162].

(B) Grain legumes can inhibit tumor promotion and progression (i.e., the transformation from initiated to neoplastic colorectal epithelial cells). First, grain legumes can increase apoptosis through the mitochondrial-mediated and death receptor-mediated pathways in neoplastic colorectal epithelial cells [88, 156] and colon cancer cell lines [163–165]. Second, grain legumes can inhibit survival of neoplastic colorectal epithelial cells by attenuating the NF-kB pathway [163–165]. Third, grain legumes can decrease proliferation of neoplastic colorectal epithelial cells [156, 163] by inducing genes that promote cell cycle arrest in G1/S and G2/M phases through p53-mediated pathways [82, 156, 165]. Fourth, grain legumes can inhibit survival and proliferation of neoplastic cells by suppressing the Akt (protein kinase B)/mTOR (mammalian target of rapamycin) pathway and upregulating the AMPK pathway, as shown for mammary carcinomas [166, 167]. In addition, upregulation of the AMPK and p53 pathway and suppression of the Akt/mTOR pathway may limit the nutrient and energy supply for the rapidly growing cancer cells and thereby inhibit tumor growth and progression [168–170]. Fifth, grain

legumes can inhibit survival and proliferation of neoplastic colorectal epithelial cells through increased butyrate production in the colon [80, 163, 171].

(C) Grain legumes can inhibit tumor promotion and progression indirectly by limiting and/or resolving inflammation. Inflammation creates a tumor microenvironment that encourages neoplastic transformations and promotes survival and proliferation of neoplastic colorectal epithelial cells. We previously showed in the Polyp Prevention Trial that the chemo-preventive effect of grain legumes against CRA recurrence is linked to a decrease in serum interleukin (IL)-6 [172]. Moreover, we demonstrated in AOM-induced ob/ob mice that navy beans and their ethanol extract decreased concomitantly colorectal neoplasia and IL-6 in serum and colon mucosa [173]. In support, others demonstrated that grain legumes can attenuate the DSS-induced increase in serum cytokine concentrations [139, 159]. Multiple mechanisms are involved in the anti-inflammatory effect of grain legumes: first, grain legume fractions can act as antioxidants and inhibit NF-kB pathways and gene expression of COX-2 and tumor necrosis factor (TNF)-α [165, 174]; second, grain legume consumption can increase mucin gene expression in the colon and thereby preserve epithelial integrity during inflammation [82, 159]; third, grain legumes can promote microbial butyrate production in the colon, which has anti-inflammatory and antitumor effects [175]; fourth, grain legumes can promote the growth of probiotic bacteria [160] and thereby inhibit the growth of inflammation-inducing bacteria [162, 176].

There is sufficient evidence in human studies, animal models, and colon cancer cell lines for multiple molecular pathways/mechanisms by which grain legume consumption inhibits early stages of colorectal tumorigenesis (i.e., tumor induction, promotion, and progression). The main molecular mechanisms involved are preventing genotoxic hits, DNA repair, inhibiting survival and proliferation of neoplastic colorectal epithelial cells, preventing, limiting, and/or resolving inflammation, and limiting nutrient supply for neoplastic colorectal epithelial cells. Identification of grain legume response biomarkers (i.e., indicators that are linked to both grain legume consumption and inhibition of colorectal tumorigenesis such as IL-6) will be important to evaluate the efficacy of grain legumes in future long-term intervention studies in humans. Grain legume consumption alters the composition and metabolism of colon microbiota, cell cycle kinetics, and metabolism of colorectal epithelial cells, as well as host immune response and barrier function of the colon. Future studies are warranted to examine how grain legumes and their components alter the interplay between microbiota and host. Furthermore, more research is needed to understand the effect of grain legumes on the later stages of colorectal carcinogenesis (i.e., metastasis and invasion).

7. Conclusions

The objective of this chapter was to evaluate the evidence of a chemo-preventive role of grain legume consumption in colorectal tumorigenesis. Based on a literature review and meta-analyses, we conclude that there is limited evidence from case-control and cohort studies suggesting that daily grain legume consumption decreases CRC risk in humans. There is

considerable preclinical evidence in animal models of CRC that supports a chemo-preventive effect of dry beans in male animal CRC models. There is sufficient evidence that grain legumes contain various compounds that can exert chemo-preventive effects against colorectal tumorigenesis in animal models of CRC. This is accomplished at concentrations that are relevant for human diets through multiple molecular pathways, which are critical for induction and clonal expansion of neoplastic colorectal epithelial cells. In summary, on the basis of the current evidence, daily grain legume consumption confers chemo-preventive effects against CRC. The next step is to conduct a long-term grain legume CRC prevention intervention study in humans to further elucidate the effects of daily grain legume consumption using grain legume exposure biomarkers to validate compliance and grain legume response biomarkers to monitor efficacy.

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