META-ANALYSIS

Nuts and legumes consumption and risk of colorectal cancer: a systematic review and meta-analysis

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Abstract

Several case–control and prospective cohort studies have examined the association between the consumption of nuts and legumes and the risk of colorectal cancer. For the quantitative assessment of this association, we conducted a meta-analysis of observational studies. We searched PubMed and Web of Science databases along with hand searches for eligible studies published up to January 2022. A total of 13 studies (8 cohort studies and 5 case–control studies) on nuts consumption and 29 studies (16 cohort studies and 13 case–control studies) on legumes consumption were included in the meta-analysis. The pooled relative risks (RRs) of colorectal cancer for the highest versus lowest categories of nuts consumption and legumes consumption were 0.84 (95% CI: 0.71–0.99) and 0.90 (95% CI: 0.83–0.98), respectively. Based on the dose–response analysis, a 28 g/day (1 serving/day) increment of nut consumption was associated with a 33% lower risk of colorectal cancer, and 100 g/day (1 serving/day) increment of legumes consumption was associated with a 21% lower risk of colorectal cancer. By geographic region for nuts consumption, however, the inverse association for the highest versus lowest categories was only observed in Asia (RR = 0.44; 95% CI: 0.29–0.68) from 3 studies, and no association was found in America (RR = 1.01; 95% CI: 0.92–1.11) ($P_{difference} = 0.003$) or Europe (RR = 1.02; 95% CI: 0.84–1.25) ($P_{difference} = 0.003$). In addition, the associations tended to be weak when stratified by adjustment for confounders. Our findings suggest that the evidence for an association is currently weak, and thus further well-designed prospective studies are needed.

Keywords Nuts · Legumes · Colorectal cancer · Meta-analysis

Introduction

Colorectal cancer is the third most common cancer worldwide, with more than 1.93 million new cases of colorectal cancer incidence, and more than 935,000 deaths from colorectal cancer in 2020 [1]. In addition, the World Health Organization (WHO) estimated that in 2040, the global incidence of colorectal cancer rises to more than 3.15 million new cases and more than 1.62 million deaths from colorectal cancer [2]. The trends in colorectal cancer incidence and mortality are related to the current level of human development and might be due to adopting more Western diets and lifestyles [3].

Nuts and legumes may be considered key components of healthy diet patterns. Nuts and legumes play an important role in plant foods characterized by the Mediterranean diet due to their favorable nutrient profile [4]. Nuts included not only tree nuts, but also a wide range of nuts including peanuts. Peanuts are actually legumes, but they are often identified by consumers as part of the nuts. Nuts are a rich source of vegetable proteins, unsaturated fatty acids, vitamin B-6, vitamin E, selenium, fiber, folic acid, and other phytochemicals [5–7]. Legumes also are good sources of phytochemicals, protein fiber, and some micronutrients [4, 8]. In addition, legumes are generally low in fats, except for soybean [4]. Several previous observational studies reported that nuts and legumes were associated with a lower risk of colorectal cancer [9–17].

Three meta-analyses on nuts consumption and cancer risk have been previously conducted and included some results for the association between nuts consumption and colorectal cancer risk as part of subgroup analysis by cancer type [7, 18, 19]. However, no comprehensive meta-analysis was

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conducted to quantitatively assess the association between nuts consumption and the risk of colorectal cancer. For legumes consumption, there was a previous meta-analysis of colorectal cancer risk, which also included studies of legume fiber consumption [20]. In addition, the World Cancer Research Fund International/American Institute for Cancer Research (WCRF-AICR) conducted a meta-analysis of legumes consumption and colorectal cancer [21], which included a few studies only.

Thus, we systematically reviewed and performed a comprehensive meta-analysis of all observational studies to quantitatively evaluate the association between the consumption of nuts and legumes and risk of colorectal cancer.

Methods

Literature search and study selection

Studies published up to January 2022 were searched from PubMed and ISI Web of Science electronic databases, and the searches were limited to articles published as written in English and full-length. The search strategy included the following keywords: "(nut OR almond OR cashew OR tree nut OR peanut OR pecan OR pine nut OR pistachio OR macadamia OR hazelnut OR walnut OR brazil nut OR legume OR soy OR bean OR pea OR soybean OR tofu OR soymilk OR pulse OR lentils OR miso OR natto) AND (colorectal OR colon OR rectal OR rectum) AND (cancer OR neoplasm OR carcinoma OR tumor)". In addition, we supplemented by a manual search of reference lists of retrieved articles and reviews to identify additional qualified studies. The searches were limited to articles published as written in English and full-length. Inclusion criteria were as follows: (1) case–control or cohort studies; (2) studies that reported the association between the consumption of nuts or legumes and the risk of colorectal cancer; (3) studies that reported relative risks (RRs) and confidence intervals (CIs). If more than one article reported the results from the same study, we selected the study which included more cases. In addition, we excluded a study that had no adjustment for any confounder [9].

Data extraction

Data extraction was conducted independently by two investigators (S.J. and Y.J.) using the meta-analysis of observational studies in epidemiology (MOOSE) guidelines [22], and any disagreements were addressed by checking the original reports and discussion. The following information was extracted from each study: first author's last name, year of publication; country and study name; study design; follow-up period or study period; baseline age; sex; number of cases

and controls/participants or person-time; each category of nuts or legumes consumption; RRs and 95% CIs for all categories of nuts and legumes consumption; adjustment for potential confounders. If studies reported several RRs, we used the RR that reflected maximally adjusted for potentially confounding variables. If some studies assessed more than one type of legumes products, we used the RR that was the most representative of overall legumes consumption and legumes that were the most commonly consumed.

Statistical analysis

To estimate pooled RRs and its 95% CIs for the highest versus lowest category of nuts and legumes consumption, we combined a natural logarithm of the RR from the original study, using the random-effects models by DerSimonian and Laird, which incorporate both within- and between-study variations [23]. If the study separately reported by cancer site, we combined the two results using a fixed-effect model to obtain an overall estimate of colorectal cancer or colon cancer first and then combined with other studies [10, 16, 17, 24–28]. In addition, if the study separately reported according to sex [11, 14, 16, 24, 26, 29–33], different ages [34], race [35] or family history [36, 37], we also combined the two results using a fixed-effect model to obtain an overall estimate first and then combined with other studies. To investigate whether the association between consumption of nuts and legumes and risk of colorectal cancer differed by study design (cohort/case–control), sex, cancer site (colon/proximal colon/distal colon/rectal), geographical region (America/Europe/Asia/Oceania), we conducted a subgroup analysis when separated data were available.

Linear dose–response analyses using the generalized least-squares trend (GLST) estimation method by Greenland and Longnecker were conducted to estimate study-specific slopes across categories of nuts and legumes consumption [38–40]. We used the median value for each exposure category of nuts and legumes consumption. If the upper category was open-ended, we assumed the same amplitude as the previous category. Studies with less than 3 exposure categories or missing data on the number of cases and participants for each exposure category were excluded from the dose–response analysis. For studies that reported exposure units other than grams per day, we defined one serving as 28 g for nuts and 100 g for legumes according to the standard of the previous study converting these into grams per day [18, 41].

Statistical heterogeneity across the included studies was assessed using the Q statistic [42], and inconsistency was quantified by I^2 statistic [43]. Sensitivity analyses were conducted by excluding each study at a time. Potential publication bias was evaluated with Begg's [44] and Egger's tests [45]. To detect the effect of possible missing studies on

the overall effect, we used Duval and Tweedie trim-and-fill methods [46]. A two-tailed P value < 0.05 was considered statistically significant. All statistical analyses were performed by using Stata/SE version 14.2 Software (StataCorp, College Station, TX, USA).

Results

Study characteristics

For nuts consumption, a total of 13 studies including 8 prospective cohort studies [12, 14, 29, 47–50] with 9546 cases and 5 case–control studies [10, 17, 34, 35, 51] with 2914 cases were included in the meta-analyses (Fig. 1). For legumes consumption, a total of 29 studies including 16 prospective cohort studies [12, 14, 15, 26, 28, 30–32, 36, 52–57] with 13,631 cases and 13 case–control studies [10, 11, 13, 16, 24, 25, 27, 33, 35, 37, 51, 58–60] with 7275 cases were included in the meta-analyses. The characteristics of the included studies are summarized in Tables 1 and 2. By geographic region, regarding nuts consumption, seven studies were performed in America, three studies in Europe, and three studies in Asia. Regarding legumes consumption, ten

studies were performed in America, four studies in Europe, fourteen studies in Asia, and one study in Oceania. Most of the studies adjusted for age, total energy intake, alcohol consumption, smoking, body mass index (BMI, kg/m^2), and physical activity.

Nuts consumption and colorectal cancer

A total of thirteen studies including 12,460 cases and 926,327 participants investigated the association between nuts consumption and risk of colorectal cancer (Table 1). The pooled RR for highest versus lowest categories of nuts consumption was 0.84 (95% CI: 0.71–0.99), with some evidence of heterogeneity ($I^2 = 82.4\%$, $P < 0.001$) (Fig. 2, Table 3). No significant associations were found when stratified by study design or sex, and the meta-regression analysis showed no significant differences ($P_{difference} > 0.5$ for all comparisons). By cancer site, a significant inverse association was shown in colon (RR = 0.78; 95% CI: 0.63–0.96) and rectal cancer (RR = 0.71; 95% CI: 0.51–0.98). Based on the meta-regression analyses, there was no significant difference with cancer site ($P_{difference} > 0.7$ for all comparisons). By geographic region, however, there was some difference in RRs. The inverse association between nut consumption
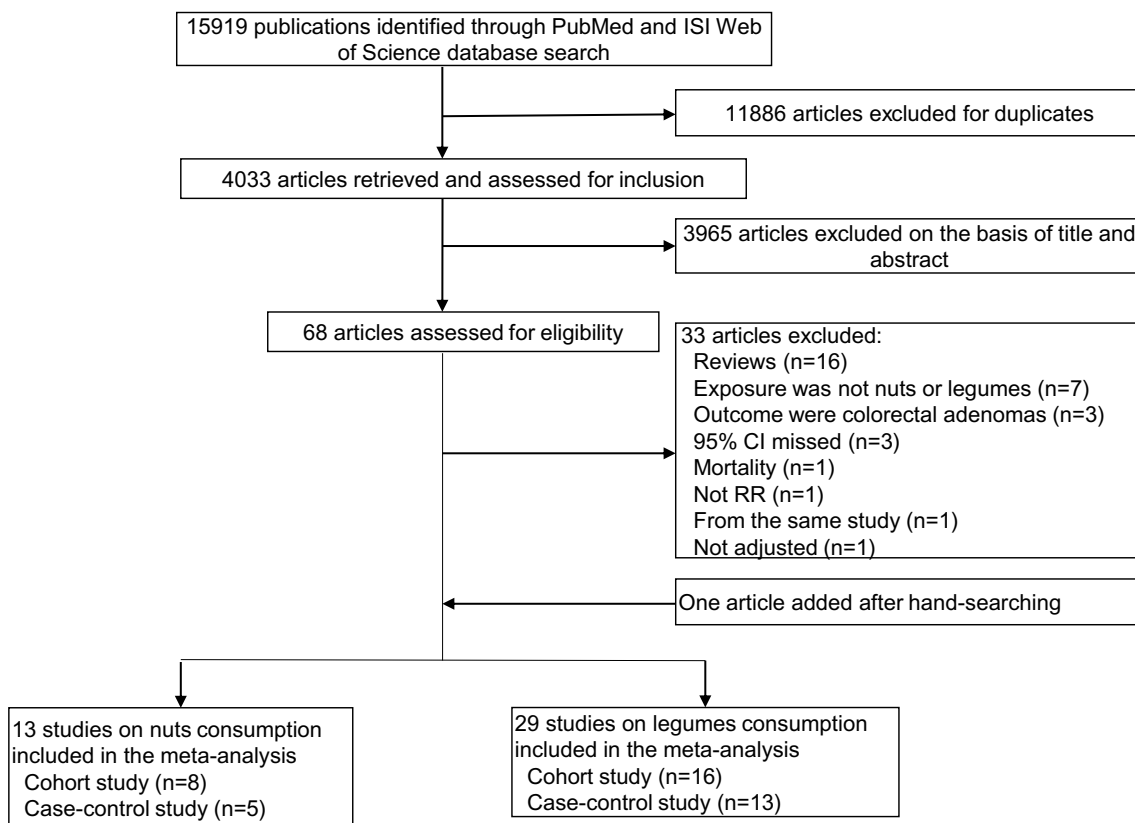

Fig. 1 Flow diagram of the study selection

Table 1 Characteristics of the prospective cohort/case–control studies included in the meta-analysis of nuts consumption and colorectal cancer

First author, year	Country (study name)	Study design (follow-up period)	Age (years)	Subjects	Exposure category	Adjustment for covariates
Singh, 1998 [12]	USA (California Seventh-Day Adventists)	Cohort (6 y)	≥25	157/32051	Nuts Never to <1 (ref), 1–4, >4/week	Age, sex, BMI, physical activity, parental history of colon cancer, current smoking, past smoking, alcohol consumption, and aspirin use
Jenab, 2004 [47]	Europe (European Prospective Investigation into Cancer and Nutrition study)	Cohort (4.8 y)	51.2	1329/478040	Nuts 0.0 (ref), 0.0–0.8, >0.8–2.3, >2.3–6.2, >6.2 g/d	Age, sex, energy from alcohol, energy from fat, energy from carbohydrates, proteins, height, weight, intake of fruits, intake of dietary fiber, physical activity, and duration of smoking
Lin, 2004 [48]	USA (Women's Health Study)	Cohort (8.7 y)	≥45	202/37547	Nuts 0 (ref), 0.07, 0.13, 0.28, 0.64 servings/day	Age, random treatment assignment, BMI, family history of CRC, history of colorectal polyps, physical activity, cigarette smoking, alcohol consumption, postmenopausal hormone therapy, and total energy intake
Yeh, 2006 [14]	Taiwan (Taiwan community-based cancer screening cohort)	Cohort (10 y)	30–65	107/23943	Peanut products 0–1 (ref), 2 + meals/week	Age, resident area, cigarette smoking, BMI, pickled foodstuffs
Yang, 2016 [49]	USA (Nurses' Health Study)	Cohort (30 y)	30–55	1503/75680	Nuts 0 (ref), 0.01–0.09, 0.10–0.19, ≥0.20 servings/day	Age, physical activity, family history of CRC, history of previous lower endoscopy, history of ulcerative colitis, history of polyps, aspirin use, multivitamin use, pack-years of smoking, alcohol intake and total energy intake, BMI, and history of diabetes mellitus
Nieuwenhuis, 2020 [29]	Netherlands (Netherlands Cohort Study)	Cohort (20.3 y)	55–69	3567/120852	Nuts 0 (ref), 0.1–<5, 5–<10, 10+ g/day	Age, cigarette smoking, BMI, non-occupational physical activity, educational level, family history of CRC, total energy intake and alcohol consumption

Table 1 (continued)

First author, year	Country (study name)	Study design (follow-up period)	Age (years)	Subjects	Exposure category	Adjustment for covariates
Fang, 2021 [50]	USA (Health Professionals Follow-up Study, Nurses' Health Study I, Nurses' Health Study II)	Cohort (HPFS, 26.8 y; NHS I,35.4 y; NHS II, 26 y)	HPFS, 40-75 y; NHS I, 30-55 y; NHS II, 25-42 y	4184/226392	Nuts Never or almost never (ref), <1, 1, 2–4, ≥5 servings/week	Age, sex, total energy intake, race/ethnicity, height, smoking status and cigarettes per day, smoking pack-years, age at initiation, years since quitting, alcohol drinking, total activity, menopausal status, postmenopausal hormone use, aspirin use, multivitamin use, and family history of cancer endoscopy screening, BMI, intake of fiber, folate, calcium, and red/processed meat, history of diabetes, and periodontal disease
Young, 1988 [34]	USA	Case–control	≥18	353/618	Peanut butter 1 (ref), 20/month	Age, sex
Hoshiyama, 1993 [10]	Japan	Case–control	40–69	181/653	Nuts None (ref), ≤2, ≥3/month	Age, sex, food items
Evans, 2002 [51]	UK	Case–control	36–100	512/512	Peanuts non/irregular consumers (ref), regular consumers	Age, sex, geographically by postal code, energy, red meat, alcohol, calcium, protein, fat, regular aspirin consumption and exercise
Williams, 2009 [35]	USA	Case–control	40–79	945/959	Nuts Whites: 0.2 (ref), 0.7, 1.5, 4.2 servings/week. African-Americans: 0.1 (ref), 0.4, 0.9, 2.4 servings/week	Age, sex, education, income, BMI 1 year ago, physical activity, family history, non-steroidal anti-inflammatory drug use, and total energy intake
Lee, 2018 [17]	Korea	Case–control	M: cases: 57.2, control: 56.6; F: cases: 55.3, control: 54.9	923/1846	Nuts None (ref), <1, 1–3, ≥3 serving/week	Age, education, alcohol consumption, regular exercise, BMI, red meat, fruit and vegetable intake, calcium, vitamin D, and total energy intake

M male, *F* female, *CRC* colorectal cancer

Table 2 Characteristics of the prospective cohort/case–control studies included in the meta-analysis of legumes consumption and colorectal cancer

First author, year	Country (study name)	Study design (follow-up period)	Age (years)	Subjects	Exposure category	Adjustment for covariates
Sellers, 1998 [36]	USA (Iowa Women's Health Study)	Cohort (10 y)	55–69	241/35,216	Legumes ≤2 (ref), 2.1–3.5, > 3.5 servings/week	Age, total energy intake, and history of rectal colon polyps
Singh, 1998 [12]	USA (California Seventh-Day Adventists)	Cohort (6 y)	≥25	157/32,051	Legumes Never to <1 (ref), 1–2, > 2/week	Age, sex, BMI, physical activity, parental history of colon cancer, current smoking, past smoking, alcohol consumption, and aspirin use
Michels, 2000 [28]	USA (Nurses' Health Study, Health Professionals' Follow-up Study)	Cohort (NHS, 16 y; HPFS, 10 y)	30–75	937/136,089	Legumes <1 (ref), 1, 2, 3, ≥4 servings/week	Age, family history of CRC, sigmoidoscopy, height, BMI, pack-years of smoking, alcohol intake, physical activity, menopausal status, postmenopausal hormone use, aspirin use, vitamin supplement intake, total caloric intake, and red meat consumption
Voorrips, 2000 [26]	Netherlands (Netherlands Cohort Study)	Cohort (6.3 y)	55–69	910/2953	Legumes M: 11 (ref), 22, 30, 40, 62 g/day F: 10 (ref), 18, 26, 37, 58 g/day	Age, family history of CRC, and category of alcohol intake
Flood, 2002 [52]	USA (Breast Cancer Detection Demonstration Project)	Cohort (8.7 y)	61.86	485/45,490	Beans <0.001 (ref), 0.006, 0.016, 0.034, 0.080 servings/1000 kJ/d	Age, total energy intake, multivitamin supplement use, BMI, height, use of nonsteroidal anti-inflammatory drugs, smoking status, education level, physical activity, and intakes of fruit, grains, red meat, calcium, vitamin D, and alcohol
Lin, 2005 [53]	USA (Women's Health Study)	Cohort (10 y)	≥45	223/36,976	Legumes 0.1 (ref), 0.2, 0.4, 0.5, 0.9 serving/day	Age, randomized treatment assignment, BMI, family history of CRC in a first degree relative, history of colon polyps, physical activity, smoking status, baseline aspirin use, red meat intake, alcohol consumption, total energy intake, menopausal status and baseline post-menopausal HT use, folate intake and multivitamin use
Yeh, 2006 [14]	Taiwan (Taiwan community-based cancer screening cohort)	Cohort (10 y)	30–65	107/23,943	Bean products 0–1 (ref), 2 + meals/week	Not specified

Table 2 (continued)

First author, year	Country (study name)	Study design (follow-up period)	Age (years)	Subjects	Exposure category	Adjustment for covariates
Oba, 2007 [30]	Japan (Takayama study)	Cohort (8 y)	≥35	213/30,221	Soy product M: 49.22 (ref), 85.52, 141.09 g/day F: 46.29 (ref), 79.60, 128.03 g/day	Age, height, alcohol intake, smoking status, BMI, physical exercise, coffee intake, and use of hormone replacement therapy
Park, 2007 [31]	USA (NIH–AARP Diet and Health Study)	Cohort (5 y)	50–71	2972/488,043	Legumes M: 0.08 (ref), 0.17, 0.27, 0.40, 0.69 servings/1,000 kcal per day F: 0.09 (ref), 0.19, 0.30, 0.45, 0.81 servings/1,000 kcal per day	Age, education, physical activity, smoking, alcohol consumption, and intake of red meat, dietary calcium, and total energy
Akhter, 2008 [32]	Japan (Japan Public Health Center–based prospective study)	Cohort (5 y)	45–74	886/83,063	Soy food Lowest (ref), 2nd, 3rd, Highest	Age, public health center area, history of diabetes mellitus, BMI, leisure time physical activity, cigarette smoking, alcohol drinking, and intake of vitamin D, dairy products, meat, vegetable, fruit, and fish, menopausal status, and current use of female hormones
Butler, 2008 [54]	Singapore (Singapore Chinese Health Study)	Cohort (10 y)	45–74	961/61,321	Soy foods Q1 (ref), Q4	Age at interview, sex, dialect group, interview year, diabetes at baseline, smoking history, BMI, alcohol intake, education, any weekly physical activity, first-degree relative diagnosed with CRC, and total daily energy intake
Yang, 2009 [15]	China (Shanghai Women's Health Study)	Cohort (6.4 y)	40–70	321/68,412	Soy foods ≤12.8 (ref), 12.9–21.0, >21 g/d	Age, education, household income, physical activity, BMI, menopausal status, family history of CRC, total calorie intake, and average intakes of fruit, vegetables, red meat, nonsoy calcium, nonsoy fiber, and nonsoy folic acid and was stratified by birth year

Table 2 (continued)

First author, year	Country (study name)	Study design (follow-up period)	Age (years)	Subjects	Exposure category	Adjustment for covariates
Bamia, 2013 [55]	Europe (European Prospective Investigation into Cancer and nutrition study)	Cohort (11.6 y)	25–70	4355/480,308	Legumes 0 (ref), 5.7, 30.1 g/day	Age, sex, age at enrolment, BMI, physical activity, educational level, smoking status at enrolment and mutually adjusted for all nutritional variables
Vogtmann, 2013 [56]	China (Shanghai Men's Health Study)	Cohort (6.3 y)	40–74	398/61,274	Legumes <16.99 (ref), 16.99–27.62, 27.63–39.36, 39.37–58.23, ≥58.24 g/day	Age, total energy intake, red meat intake, total meat intake, education, income, occupation, smoking status, alcohol consumption, BMI, MET hours of exercise participation, history of diabetes mellitus, and family history of CRC
Jones, 2017 [57]	UK (UK Women's Cohort Study)	Cohort (17.4 y)	52	465/35,372	Legumes 12 (ref), 31, 73 g/day	Age, BMI, energy intake, physical activity, smoking status, socioeconomic status, and family history of CRC
Hoshiyama, 1993 [10]	Japan	Case–control	40–69	181/653	Soybean products ≤4 (ref), 5–7, ≥8/week	Age, sex, food items
Steinmetz, 1993 [11]	Australia	Case–control	30–74	220/438	Legumes M: 0 (ref), 0.1–0.4, 0.5–0.9, ≥1.0 serving/week F: 0 (ref), 0.1–0.5, ≥0.6 serving/week	Protein intake, age at first live birth, BMI, and alcohol intake
Inoue, 1995 [24]	Japan	Case–control	24–88	432/31,782	Bean curd ≤3–4 (ref), >3–4 times/week	Age
Le Marchand, 1997 [33]	USA	Case–control	case:66 control:64	1192/1192	Legumes and soy products Q1 (ref), Q2, Q3, Q4	Age, family history of CRC, alcoholic drinks per week, pack years of cigarette smoking, lifetime recreational activity, BMI 5 years earlier, and intake of calories, calcium, eggs, and NSP from vegetables
Nishi, 1997 [25]	Japan	Case–control	≥30	330/660	Tofu <3 (ref), ≥3/week	Age, sex, registered residence
Deneo-Pellegrini, 2002 [13]	Uruguay	Case–control	≥30	484/1452	Legumes Q1 (ref), Q2, Q3, Q4	Age, residence, urban/rural status, education, family history of colon cancer for first-degree relatives, BMI, total energy, and red meat intakes

Table 2 (continued)

First author, year	Country (study name)	Study design (follow-up period)	Age (years)	Subjects	Exposure category	Adjustment for covariates
Evans, 2002 [51]	UK	Case–control	36–100	512/512	Legumes 1 (ref), 2, 4, 5 servings/week	Age, sex, geographically by postal code, energy, red meat, alcohol, calcium, protein, fat, regular aspirin consumption and exercise
Seow, 2002 [58]	Singapore	Case–control	case: 64.9 control: 56.9	121/222	Soy and legumes <78 (ref), 78–<234, ≥234 portions per year	Age, family history of CRC, sex, smoking history, years of formal education, and usual number of hours of moderate/vigorous exercise per week
Huang, 2004 [37]	Japan	Case–control	≥18	1352/50,706	Bean curd <3 (ref), ≥3/week	Age and sex
Williams, 2009 [35]	USA	Case–control	40–79	945/959	Beans and peas Whites: 0.1 (ref), 0.6, 1.2, 2.7 servings/week African-Americans: 0.1 (ref), 0.6, 1.3, 2.6 servings/week	Age, sex, education, income, BMI 1 year ago, physical activity, family history, nonsteroidal anti-inflammatory drug use, and total energy intake
Budhathoki, 2011 [27]	Japan	Case–control	20–74	816/815	Soy foods 5.4 (ref), 8.8, 13.1, 18.5, 26.8 g/day	Age, resident area, parental colorectal cancer, smoking, alcohol use, BMI, type of job, leisure-time physical activity, and energy-adjusted intakes of calcium and n-3 polyunsaturated fatty acids
Abu Mweis, 2015 [59]	Jordan	Case–control	≥18	84/154	Lentils <1 (ref), ≥1/week	Age, sex, total energy, metabolic equivalent, smoking, education level, marital status, work, income, and family history of CRC
Shin, 2015 [16]	Korea	Case–control		901/2669	Soy products M: <40.34 (ref), 40.34–<64.64, 64.64–<105.03, ≥105.03 g/day F: <42.77 (ref), 42.77–<70.29, 70.29–<113.66, ≥113.66 g/day	Age, education, alcohol consumption, and regular exercise
Azzeh, 2017 [60]	Saudi Arabia	Case–control	40–75	137/164	Legumes <1 (ref), 1–2, 3–5, > 5 servings/week	Age, sex, BMI, education, income, employment, smoking, marital status, physical activity, and family history of CRC

M male, *F* female, *CRC* colorectal cancer

Study

ID

RR (95% CI)

Singh et al. (1998)(CC)   0.68 (0.45, 1.03)

Jenab et al. (2004)   0.91 (0.75, 1.11)

Lin et al. (2004)(F)   1.05 (0.67, 1.64)

Yeh et al. (2006)   0.60 (0.40, 0.90)

Nieuwenhuis et al. (2020)   0.95 (0.82, 1.11)

Fang et al. (2021)(HPFS,NHS,NHSII)   1.07 (0.91, 1.25)

Young et al. (1988)(CC)   1.03 (0.96, 1.11)

Hoshiyama et al. (1993)   0.49 (0.29, 0.83)

Evans et al. (2002)   1.37 (1.01, 1.85)

Williams et al. (2009)(RC)   0.88 (0.64, 1.21)

Lee et al. (2018)   0.30 (0.20, 0.45)

Overall (I-squared = 82.4%, p = 0.000)   0.84 (0.71, 0.99)

NOTE: Weights are from random effects analysis

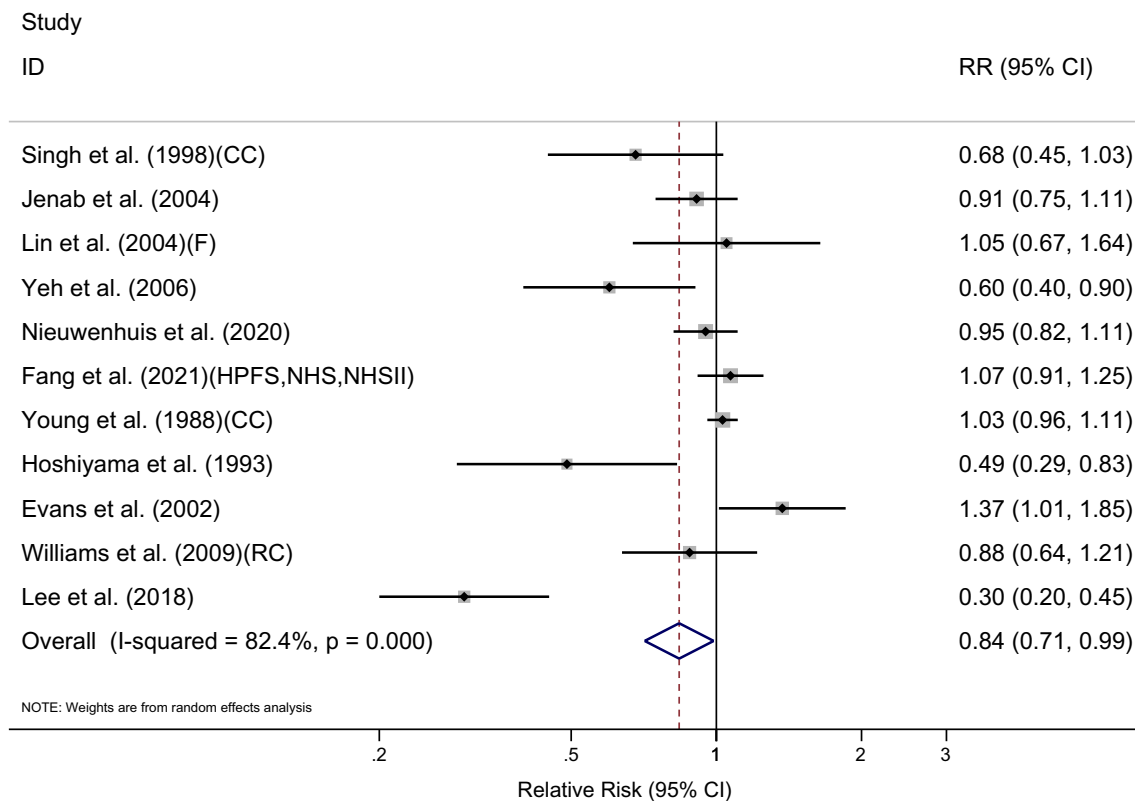.2   .5   1   2   3

Relative Risk (95% CI)

Fig. 2 Forest plot of colorectal cancer risk for the highest versus lowest categories of nuts consumption

and colorectal cancer risk was only observed in Asia (RR = 0.44; 95% CI: 0.29–0.68), while no association was found in America (RR = 1.01; 95% CI: 0.92–1.11) ($P_{\text{difference}}$ for America vs. Asia = 0.003) or Europe (RR = 1.02; 95% CI: 0.84–1.25) ($P_{\text{difference}}$ for Europe vs. Asia = 0.003). Furthermore, no heterogeneity was observed in the studies stratified by region. Regarding adjustment for confounders, there was no significant difference with energy intake, alcohol intake, smoking, BMI, physical activity, or dietary factors ($P_{\text{difference}} > 0.4$ for all comparisons). Nine studies [12, 17, 29, 35, 47, 48, 50] were included in the dose–response analysis for nuts consumption and risk of colorectal cancer. A 28 g/day (1 serving/day) increment of nuts consumption was associated with a 33% lower risk of colorectal cancer (RR = 0.67; 95% CI: 0.45–0.98).

Legumes consumption and colorectal cancer

A total of twenty-nine studies including 20,906 cases and 1,688,603 participants investigated the association between legumes consumption and risk of colorectal cancer (Table 2). The pooled RR of colorectal cancer for the highest versus lowest categories of legumes intake was 0.90 (95% CI: 0.83–0.98), with some evidence of

heterogeneity ($I^2 = 56.5\%$, $P < 0.001$) (Fig. 3, Table 4). In the stratified analysis by study design, we found no significant association, and the meta-regression analysis showed no significant differences ($P_{\text{difference}} = 0.31$). By sex, a significant inverse association was found in women (RR = 0.86; 95% CI: 0.75–0.99), but not in men (RR = 0.93; 95% CI: 0.84–1.02) ($P_{\text{difference}} = 0.64$). By cancer site, we found a significant inverse association in colon (RR = 0.89; 95% CI: 0.82–0.96) and rectal cancer (RR = 0.82; 95% CI: 0.70–0.94). By geographic region, there was a significant inverse association in Asia (RR = 0.88; 95% CI: 0.77–0.999) and Oceania (RR = 0.59; 95% CI: 0.35–0.98), while there was no significant association between in America (RR = 0.90; 95% CI: 0.78–1.04) and Europe (RR = 1.00; 95% CI: 0.85–1.19). In the meta-regression analysis, however, the pooled RRs were not significantly different with geographic region ($P_{\text{difference}}$ for America, Europe, or Oceania vs. Asia = 0.84, 0.30, and 0.24, respectively). By adjustment for confounders, we found no significant difference with energy intake, alcohol intake, smoking, BMI, physical activity, or dietary factors ($P_{\text{difference}} > 0.1$ for all comparisons). Fourteen studies [12, 15, 16, 27, 28, 30, 35, 36, 53, 56–58, 60] were included in the dose–response analysis for legumes consumption

Table 3 Summary of pooled relative risks (RR) of colorectal cancer risk for nuts consumption

	No. of studies	RR (95% CI)	Heterogeneity	$P_{difference}$
High versus low nuts intake				
All studies	13	0.84(0.71–0.99)	$I^2 = 82.4\%, P < 0.001$	
Study design				
Cohort	8	0.91(0.79–1.05)	$I^2 = 49.1\%, P = 0.08$	0.57
Case–control	5	0.74(0.48–1.12)	$I^2 = 91.4\%, P < 0.001$	
Sex				
Men	5	0.80(0.56–1.15)	$I^2 = 85.5\%, P < 0.001$	0.998
Women	7	0.82(0.64–1.05)	$I^2 = 66.3\%, P = 0.01$	
Cancer site				
Colon	7	0.78(0.63–0.96)	$I^2 = 83.0\%, P < 0.001$	0.83[a]
Proximal	4	0.89(0.68–1.17)	$I^2 = 72.3\%, P = 0.01$	0.75[b]
Distal	4	0.74(0.52–1.05)	$I^2 = 85.0\%, P < 0.001$	
Rectal	6	0.71(0.51–0.98)	$I^2 = 77.4\%, P < 0.001$	
Geographic region				
Asia	3	0.44(0.29–0.68)	$I^2 = 65.4\%, P = 0.06$	
America	7	1.01(0.92–1.11)	$I^2 = 17.4\%, P = 0.30$	0.003[c]
Europe	3	1.02(0.84–1.25)	$I^2 = 63.0\%, P = 0.07$	0.003[c]
Adjustment for confounders				
Strong adjustment[d]	5	1.01(0.91–1.12)	$I^2 = 0\%, P = 0.56$	0.28
Weak adjustment[d]	8	0.75(0.58–0.97)	$I^2 = 87.3\%, P < 0.001$	
Energy intake				
Yes	9	0.88(0.70–1.12)	$I^2 = 84.8\%, P < 0.001$	0.43
No	4	0.70(0.48–1.04)	$I^2 = 82.2\%, P = 0.001$	
Alcohol intake				
Yes	8	0.84(0.62–1.14)	$I^2 = 88.0\%, P < 0.001$	0.80
No	5	0.83(0.67–1.02)	$I^2 = 73.2\%, P = 0.01$	
Smoking				
Yes	8	0.91(0.79–1.05)	$I^2 = 49.1\%, P = 0.08$	0.57
No	5	0.74(0.48–1.12)	$I^2 = 91.4\%, P < 0.001$	
BMI				
Yes	9	0.75(0.58–0.99)	$I^2 = 84.7\%, P < 0.001$	0.45
No	4	0.97(0.77–1.21)	$I^2 = 76.0\%, P = 0.01$	
Physical activity				
Yes	10	0.86(0.69–1.07)	$I^2 = 83.3\%, P < 0.001$	0.55
No	3	0.70(0.42–1.17)	$I^2 = 85.3\%, P = 0.001$	
Dietary factors				
Yes	8	0.73(0.51–1.04)	$I^2 = 89.8\%, P < 0.001$	0.41
No	5	0.98(0.89–1.07)	$I^2 = 19.6\%, P = 0.29$	
Increment of 28 g/day	9	0.67(0.45–0.98)	$I^2 = 85.8\%, P < 0.001$	

[a]*P* value for difference in RRs of nut consumption for colon cancer versus rectal cancer

[b]*P* value for difference in RRs of nut consumption for proximal colon cancer versus distal colon cancer

[c]*P* value for difference in RRs of nut consumption for America versus Asia, and Europe versus Asia

[d]Adjustment for at least age, energy intake, alcohol intake, smoking status, BMI, and physical activity is considered as strong adjustment. Otherwise, it is considered as weak adjustment

and risk of colorectal cancer. A 100 g/day (1 serving/day) increment of legumes consumption was associated with a 21% lower risk of colorectal cancer (RR = 0.79; 95% CI: 0.64–0.97).

Publication bias

For the analysis of nuts consumption and risk of colorectal cancer, there was no evidence of publication bias in Egger's (*P* value for bias = 0.06) and Begg's test (*P* value
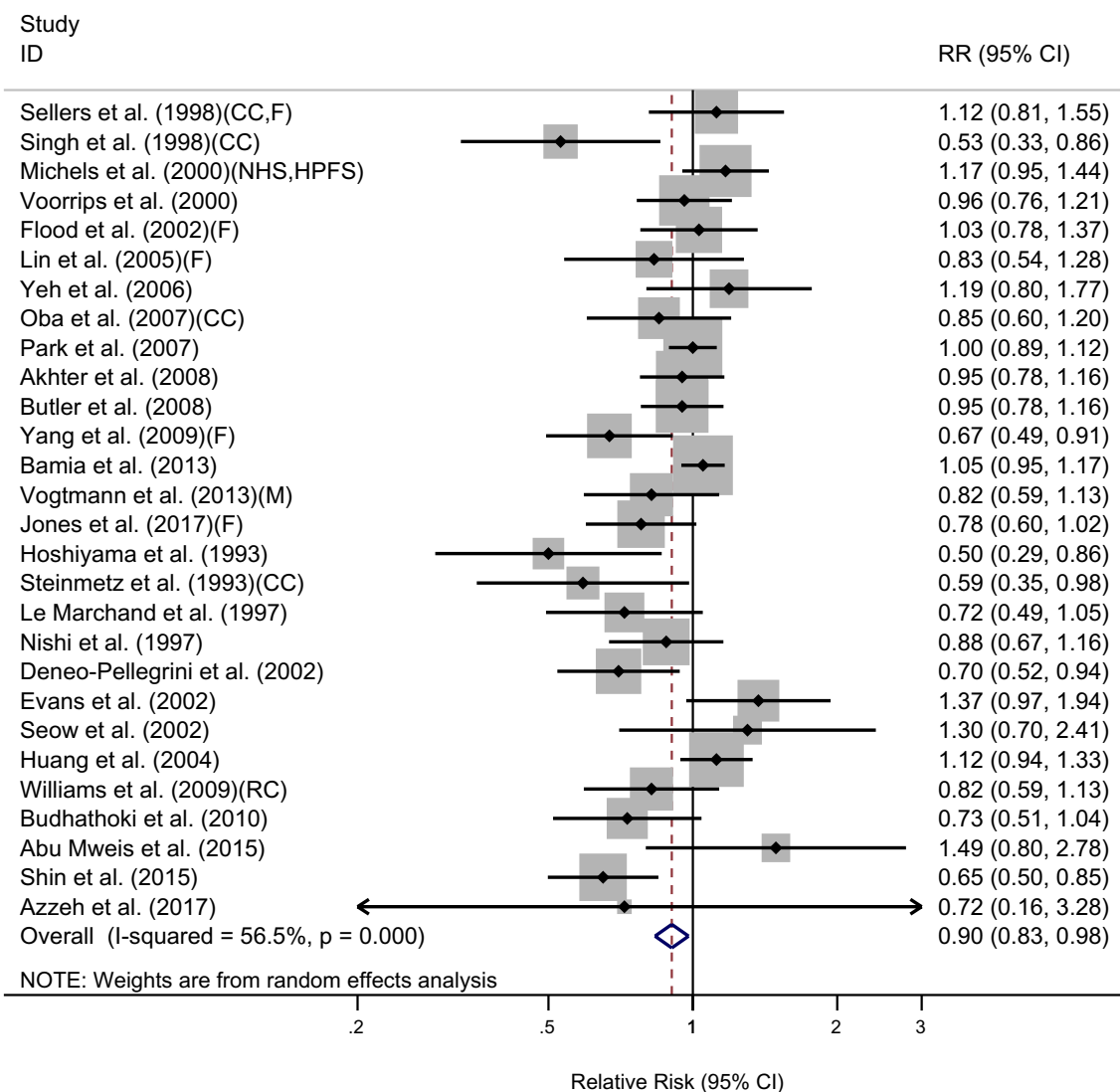
Study
ID   RR (95% CI)

Study ID	RR (95% CI)
Sellers et al. (1998)(CC,F)	1.12 (0.81, 1.55)
Singh et al. (1998)(CC)	0.53 (0.33, 0.86)
Michels et al. (2000)(NHS,HPFS)	1.17 (0.95, 1.44)
Voorrips et al. (2000)	0.96 (0.76, 1.21)
Flood et al. (2002)(F)	1.03 (0.78, 1.37)
Lin et al. (2005)(F)	0.83 (0.54, 1.28)
Yeh et al. (2006)	1.19 (0.80, 1.77)
Oba et al. (2007)(CC)	0.85 (0.60, 1.20)
Park et al. (2007)	1.00 (0.89, 1.12)
Akhter et al. (2008)	0.95 (0.78, 1.16)
Butler et al. (2008)	0.95 (0.78, 1.16)
Yang et al. (2009)(F)	0.67 (0.49, 0.91)
Bamia et al. (2013)	1.05 (0.95, 1.17)
Vogtmann et al. (2013)(M)	0.82 (0.59, 1.13)
Jones et al. (2017)(F)	0.78 (0.60, 1.02)
Hoshiyama et al. (1993)	0.50 (0.29, 0.86)
Steinmetz et al. (1993)(CC)	0.59 (0.35, 0.98)
Le Marchand et al. (1997)	0.72 (0.49, 1.05)
Nishi et al. (1997)	0.88 (0.67, 1.16)
Deneo-Pellegrini et al. (2002)	0.70 (0.52, 0.94)
Evans et al. (2002)	1.37 (0.97, 1.94)
Seow et al. (2002)	1.30 (0.70, 2.41)
Huang et al. (2004)	1.12 (0.94, 1.33)
Williams et al. (2009)(RC)	0.82 (0.59, 1.13)
Budhathoki et al. (2010)	0.73 (0.51, 1.04)
Abu Mweis et al. (2015)	1.49 (0.80, 2.78)
Shin et al. (2015)	0.65 (0.50, 0.85)
Azzeh et al. (2017)	0.72 (0.16, 3.28)
Overall (I-squared = 56.5%, p = 0.000)	0.90 (0.83, 0.98)

NOTE: Weights are from random effects analysis

Relative Risk (95% CI)

Fig. 3 Forest plot of colorectal cancer risk for the highest versus lowest categories of legumes consumption

for bias = 0.09). For the analysis of legumes consumption and risk of colorectal cancer, Egger's test suggested some evidence of bias (*P* value for bias = 0.02), but not in Begg's test (*P* value for bias = 0.21). When we used the trim-and-fill method to examine the influence of potential publication bias, the pooled RR did not alter, indicating that the results were not affected by publication bias.

Discussion

The present meta-analysis of observational studies assessed the association between nuts and legumes consumption and colorectal cancer risk. This meta-analysis indicated that people in the highest category of nuts and legumes consumption

had a decreased risk of colorectal cancer by 16% and 10%, respectively, compared with those in the lowest category. In addition, we found the inverse association tends to be stronger in Asia, especially for nuts consumption. The results of the dose–response analysis also supported these associations.

A few previous meta-analyses have been conducted to assess the association between nuts consumption and cancer risk, and the association of nuts consumption with colorectal cancer risk was examined in the form of subgroup analysis only [7, 18, 19]. For legumes consumption, two meta-analyses were conducted to examine the association with colorectal cancer risk [20, 21]. One of the meta-analyses from the WCRF-AICR continuous update project included six studies, and due to the limited number of studies, it

Table 4 Summary of pooled relative risks (RR) of colorectal cancer risk for legumes consumption

	No. of Studies	RR (95% CI)	Heterogeneity	$P_{\text{difference}}$
High versus low legumes intake				
All studies	29	0.90(0.83–0.98)	$I^2=56.5\%, P<0.001$	
Study design				
Cohort	16	0.95(0.88–1.03)	$I^2=41.8\%, P=0.05$	0.31
Case–control	13	0.85(0.71–1.00)	$I^2=64.9\%, P=0.001$	
Sex				
Men	13	0.93(0.84–1.02)	$I^2=24.8\%, P=0.19$	0.64
Women	17	0.86(0.75–0.99)	$I^2=62.1\%, P<0.001$	
Cancer site				
Colon	17	0.89(0.82–0.96)	$I^2=15.7\%, P=0.27$	0.38[a]
Proximal	5	0.91(0.68–1.22)	$I^2=32.2\%, P=0.21$	0.56[b]
Distal	5	0.80(0.60–1.05)	$I^2=49.3\%, P=0.10$	
Rectal	14	0.82(0.70–0.94)	$I^2=49.0\%, P=0.02$	
Geographic region				
Asia	14	0.88(0.77–0.999)	$I^2=53.8\%, P=0.01$	
America	10	0.90(0.78–1.04)	$I^2=57.9\%, P=0.02$	0.84[c]
Europe	4	1.00(0.85–1.19)	$I^2=58.8\%, P=0.06$	0.30[c]
Oceania	1	0.59(0.35–0.98)	$I^2=-, P=-$	0.24[c]
Adjustment for confounders				
Strong adjustmentd[d]	8	0.92(0.80–1.06)	$I^2=36.9\%, P=0.15$	0.83
Weak adjustmentd[d]	20	0.89(0.80–0.98)	$I^2=62.9\%, P<0.001$	
Energy intake				
Yes	16	0.91(0.82–1.02)	$I^2=52.7\%, P=0.01$	0.58
No	12	0.86(0.75–0.99)	$I^2=64.6\%, P=0.001$	
Alcohol intake				
Yes	16	0.89(0.80–0.99)	$I^2=55.8\%, P=0.004$	0.89
No	12	0.90(0.78–1.03)	$I^2=61.6\%, P=0.003$	
Smoking				
Yes	17	0.94(0.86–1.02)	$I^2=38.3\%, P=0.06$	0.41
No	11	0.84(0.72–0.995)	$I^2=70.1\%, P<0.001$	
BMI				
Yes	18	0.85(0.77–0.94)	$I^2=52.7\%, P=0.01$	0.13
No	10	0.98(0.85–1.13)	$I^2=63.7\%, P=0.003$	
Physical activity				
Yes	20	0.90(0.82–0.98)	$I^2=56.3\%, P=0.001$	0.92
No	8	0.89(0.74–1.08)	$I^2=64.3\%, P=0.01$	
Dietary factors				
Yes	13	0.89(0.79–1.01)	$I^2=59.8\%, P=0.004$	0.98
No	15	0.90(0.80–1.01)	$I^2=58.0\%, P=0.003$	
Increment of 100 g/day	14	0.79(0.64–0.97)	$I^2=58.9\%, P=0.004$	

[a]*P* value for difference in RRs of legume consumption for colon cancer versus rectal cancer

[b]*P* value for difference in RRs of legume consumption for proximal colon cancer versus distal colon cancer

[c]*P* value for difference in RRs of legume consumption for Europe versus America, Asia versus America, and Oceania versus America

[d]Adjustment for at least age, energy intake, alcohol intake, smoking status, BMI, and physical activity is considered as strong adjustment. Otherwise, it is considered as weak adjustment

could not conduct a stratified analysis [21]. Another meta-analysis of legumes consumption also included studies of legume fiber consumption [20]. In the present meta-analysis, we included twenty-nine studies, and thus could conduct a stratified analysis. In addition, we included

studies with legumes consumption only, and also conducted a dose–response analysis of nuts and legumes consumption.

There was some evidence of heterogeneity among the studies in the meta-analysis of nuts and legumes consumption and the risk of colorectal cancer overall. For the results of nuts consumption, the observed heterogeneity among the studies tended to disappear when stratified by geographic region. The International Nut and Dried Fruit Council Foundation (INC) reported that consumption of nuts varies by region, depending on the type of nuts [61]. Europe was the largest consumer of tree nuts, but in terms of peanut consumption, per capita, peanut consumption in Nigeria and China was much higher than in other countries [61]. In addition, in many countries, nuts were not depicted in food guides or not mentioned in brief guides or other available descriptions of food classification [62], so the consumption patterns of nuts in different countries would be different. We observed an association between nuts consumption and colorectal cancer risk only in Asia. Although it is difficult to make the definitive explanation for this result, it may be because Asians have a lower risk of nut allergy than people in Western countries [17, 63], which leads to different dietary patterns. For the type of nuts, American and European studies contained more variety of nut types than Asian studies. One Asian study only included peanut products [14], and the other Asian study only included pine nuts, peanuts, and almonds [17], while the study by Hoshiyama et al. did not mention the type of nuts [10]. The different types of nuts consumption among the studies might also explain the different results by region. However, the inverse association of nuts consumption found in Asian studies came from only three studies, and most of them were case–control studies, which are susceptible to methodological biases. For the results of legumes consumption, although the observed heterogeneity tends to disappear in colon cancer when stratified analysis by cancer site, heterogeneity could still be observed in rectal cancer. We cannot clearly explain the reasons for the observed heterogeneity, but we speculate that it may be due to the diversity of legumes. We have usually eaten dried legumes, which have matured and dried on the plant, but there are also several legumes eaten as a vegetable when they are green or sprouted, such as green beans, runner beans, and beansprouts, etc. [64]. In addition, legumes can be consumed as soy products such as tofu, soy milk, and natto, etc. Dry legumes are higher in protein than most other plant foods and are typically high in carbohydrates and dietary fiber [64], although legumes are low in fat, except for soybeans [4, 64]. On the other hand, it may be because the consumption of legumes varies by region. In East Asian diets, soybeans are the main source of phytoestrogen isoflavones, and the average isoflavone intake of the Asian population is almost 10 times higher than in Western countries [65, 66]. Therefore, more studies are needed to determine subgroups of nuts and legumes consumption in relation to colorectal cancer risk.

Several potential mechanisms of nuts and legumes consumption may reduce the risk of colorectal cancer. Nuts and legumes are a dietary source of fiber, and dietary fiber could bind and excrete potential luminal carcinogens, such as secondary bile acids and reduce fecal pH in the colon, thereby playing a critical role in colorectal cancer prevention [4, 5, 67]. In addition, high-fiber diets may decrease insulin resistance, which is a risk factor for colorectal cancer [64]. Nuts contain phytochemicals, such as resveratrol and quercetin, which can decrease the inflammatory process and prevent inflammation-induced tumors [5, 68]. Legumes also contain phytochemicals, which are isoflavones, representative anticancer components. Isoflavones have a structure similar to estrogen and selectively bind to estrogen receptors (ER) [66, 69]. When estrogen is deficient, phytoestrogens can exert an estrogenic effect [66]. Moreover, a previous meta-analysis reported that the ER-β protein protects against carcinogenesis and colorectal cancer development when activated by estrogen, indicating the potential for ER-β to act as a tumor suppressor [66, 70].

The present study had some advantages. It is the first meta-analysis to assess the association between nuts consumption and the risk of colorectal cancer. In addition, a relatively large number of studies allowed us to conduct subgroup analyses by study design, sex, cancer site, and geographic region, as well as the linear dose–response meta-analysis. The present meta-analysis included the most recent prospective cohort and case–control studies and the largest number of study participants. In addition, most of the studies included in the analysis were adjusted for confounding factors such as age, sex, energy intake, alcohol intake, smoking, BMI, and physical activity.

Despite these advantages, several potential limitations of our meta-analysis should be considered. First, the current meta-analysis included several case–control studies in addition to cohort studies, and therefore, potential methodological biases, including selection bias or recall bias, might be considered. The inverse association of nuts consumption found in three Asian studies came mostly from case–control studies, so we should be interpreted with caution. Second, some misclassification of nuts and legumes consumption may exist, which influences the results of individual studies and thus pooled estimates in this meta-analysis. In addition, the types of nuts and legumes consumed throughout each study varied widely. This wide range includes peanuts and peanut butter, which are legumes, but often identified by consumers as part of the nut, and some studies did not report detailed types of nuts and legumes consumption. Third, the cut-offs for the consumption of nuts and legumes in the highest and lowest categories varied among the studies. To address this limitation, we conducted a linear dose–response

meta-analysis as well. Fourth, for the analysis of legumes consumption and risk of colorectal cancer, we observed evidence of bias from Egger's test, but it was not observed in Begg's test. The difference in the results obtained by the two methods might be because of the greater statistical power of the regression method [71]. In addition, we conducted the trim-and-fill method, which showed that the results were not affected by publication bias. Finally, when we conducted the stratified analysis by the adjustment for confounders, it tended to show weaker associations when limited to studies with strong adjustment. Moreover, the number of well-adjusted cohort studies are still limited at present.

In conclusion, the results of the current meta-analysis suggest that the evidence for an association between nuts and legumes consumption and the risk of colorectal cancer is currently weak. We observed that the association tended to be weak when stratified by adjustment for confounders. Thus, further well-designed prospective cohort studies, especially well-adjusted for confounders, on different types of nuts and legumes consumption and different types of study populations are warranted.

Declarations

Conflict of interest The authors declare no potential conflicts of interest.

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