Association Between Consumption of Fruits and Vegetables and Risk of Colorectal Adenoma

A PRISMA-Compliant Meta-Analysis of Observational Studies

Qiwen Ben, MD, Jie Zhong, MD, Jun Liu, MD, Lifu Wang, MD, Yunwei Sun, MD, Lifen Yv, MD, and Yaozong Yuan, MD, PhD

Abstract: There have been contradictory results about the association of fruits and vegetables intake with colorectal adenoma (CRA) risk, the precursor lesion of colorectal cancer. Herein, we have conducted a meta-analysis of the published observational studies to have a clear understanding about this association.

 Eligible studies up to November 30, 2014, were identified and retrieved by searching MEDLINE and EMBASE databases along with the manual review of the reference list of the retrieved studies. The quality of the included studies was evaluated using Newcastle-Ottawa Quality Assessment Scale, and random-effects model was used to calculate summary relative risk (SRR) and corresponding 95% confidence interval (CI).

A total of 22 studies involving 11,696 CRA subjects were part of this meta-analysis. The SRR for the highest versus the lowest intake of vegetables alone was 0.91 (95% CI: 0.80–1.02, P heterogeneity = 0.025), whereas for vegetables and fruits combined, it was 0.82 (95% CI: 0.75–0.89, P heterogeneity = 0.369), and for fruits alone, it was 0.79 (95% CI: 0.71–0.88, P heterogeneity = 0.111). In addition, linear dose–response analysis also showed similar results, for example, for per 100 g/d increment of fruits, the SRR was 0.94 (95% CI: 0.92–0.97) and for vegetables it was 0.98 (95% CI: 0.96–1.01). Nonlinear association was only observed for vegetables (P nonlinearity = 0.024), but not for fruits (P nonlinearity = 0.583).

Thus, this meta-analysis suggested that fruits consumption have a significant protective effect on CRA risk, but not vegetables. Moreover, we recommend additional studies with prospective designs that use validated questionnaires and control for important confounders to further validate the overall results.

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following the criteria set out by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.30 There is no institutional review board that approved our study as all the data analyzed were from previously published studies.

Data Sources and Study Identification
Two investigators (QB and JZ) screened the published English language literature by performing computerized searches of the MEDLINE and EMBASE databases until November 30, 2014. The medical subject heading terms or keywords that were used for searching relevant articles were “adenoma” OR “polyp” OR “neoplasm” OR “neoplasia”; “colorectal” OR “colon” OR “rectal” OR “large bowel”; “nutrition” OR “diet” OR “lifestyle” OR “fruit” OR “vegetable”; and “risk” OR “incidence” OR “prevalence.” In addition, the reference lists of the identified articles were further searched for any potential relevant articles. However, we did not include abstracts or unpublished reports.

Study Selection
In the present meta-analysis, we included the studies evaluating fruit or vegetable groups classified as “all” or “total.” Two authors (QB and JZ) independently reviewed all the retrieved studies to determine if they meet the inclusion criteria and any disagreements were settled through consensus with a third investigator (YY). Studies were included in the meta-analysis, if they used a case-control, nested case-control, or cohort design; presented data for ≥3 categories of total vegetables or total fruits and incident cases of CRA; provided the data of odds ratios (ORs) or relative risks (RRs) with corresponding 95% confidence intervals (CIs) or at least present data to calculate them; and adjusted or matched the risk estimations with age at least. Non-peer-reviewed articles, animal and mechanistic studies, ecologic assessments, and correlation studies were not included for analysis. In case of several publications describing the same study, only the most recent or informative publication was included. Studies that lacked CRA-specific data or data about adenoma recurrence or growth were also excluded. We also excluded studies which described intake of only 2 categories of vegetables and/or fruit.

Data Extraction
The following information was extracted from each study independently by 2 researchers (QB and JZ), first author’s last name, study design, publication year, geographic locations, the number of cases and controls or participants, definition of controls, methods of dietary data ascertainment (types of food item and whether the assessment method had been validated), exposure classification, follow-up duration in cohort study, the RR estimates with their 95% CI for the highest versus the lowest level and adjustments for confounders. From each study, the risk estimates were extracted that have been adjusted for the greatest level and adjustments for confounders. In the absence of such data, we assigned the median in each category by calculating the average of the lower and upper boundaries. When the lowest category was open-ended, zero was considered the lowest boundary. If the highest category was open-ended, it was assumed that the open-ended interval length had the same amplitude as the adjacent interval. The dose–response results were presented per 100 g/d increment in consumption of fruits or vegetables. When studies used different measurement units (eg, grams per day or portions per week or servings per day), we standardized fruits and vegetables intake into grams per day using a standard portion size of 106 g. A potential nonlinear dose–response relationship was calculated using the best-fitting second-order fractional polynomial model,36 defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the nonlinear and linear models.36

Publication bias was measured by funnel plots, Begg adjusted rank correlation test, and Egger linear regression test.37,38 The P values of <0.10 indicated potential publication bias. If publication bias was present, we further evaluated the number of missing studies by the trim and fill method and recalculated the pooled risk estimates with the addition of those missing studies.39

Statistical Methods
All statistical analyses were performed using STATA, version 11.0 (STATA, College Station, TX) and R-package (Version 2.11.0 beta, R Development Core Team, NJ) statistical software. A 2-tailed P value of <0.05 represented significance. Random-effects model that accounts for variation between studies was used to calculate summary relative risk (SRR) (95% CI) for the highest versus lowest level, linear and nonlinear dose–responses.32 When estimates were available specifically for males and females,11,18,20 nonadvanced/advanced adenoma (NAA/AA),25 and small and large adenomas,19 they were considered as if obtained from different studies.

Heterogeneity was assessed by Cochran Q and I2 statistics. P value of <0.10 represented statistically significant heterogeneity. I2 values explained the amount of total variation among studies and a value of >50% signified severe heterogeneity while a value of <25% represented no significant heterogeneity.33 Sources of heterogeneity were explored using subgroup analyses and meta-regression analysis according to study design, sex, geographic location, type of food frequency questionnaire (FFQ), number of cases, study quality score, and confounders (adjusted for smoking, body mass index [BMI], physical activity, and dietary energy intake). Sensitivity analysis that investigated the influences of each individual study on the summary results was performed by omitting one study at a time.

Generalized least-squares trend estimation analysis34,35 was used for dose–response meta-analysis. It required the distribution of cases and person-years or noncases and RRs with known variance for at least 3 quantitative categories. Lack of this information led us to estimate the dose–response slopes using variance-weighted least squares regression analysis.34,35 For each category of intake level, the medians were assigned to corresponding RR. In the absence of such data, we assigned the median in each category by calculating the average of the lower and upper boundaries. When the lowest category was open-ended, zero was considered the lowest boundary. If the highest category was open-ended, it was assumed that the open-ended interval length had the same amplitude as the adjacent interval. The dose–response results were presented per 100 g/d increment in consumption of fruits or vegetables. When studies used different measurement units (eg, grams per day or portions per week or servings per day), we standardized fruits and vegetables intake into grams per day using a standard portion size of 106 g. A potential nonlinear dose–response relationship was calculated using the best-fitting second-order fractional polynomial model,36 defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the nonlinear and linear models.36

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RESULTS

Search Results and Study Characteristics

Based on the study selection criteria, we identified a total of 10,867 potentially relevant articles (7816 articles from the MEDLINE database and 3051 articles from the EMBASE database). In addition, 13 more articles were identified by studying the cross-reference list. Among these 10,880 articles, 77 were considered potentially relevant and their full texts were retrieved for further evaluation, and 55 were excluded for various reasons (Fig. 1). Therefore, a total of 22 articles (5 cohort and 17 case-control studies) involving 11,696 subjects with CRA were used for this meta-analysis. Table 1 and Table 2 depict the characteristics of these studies. All these studies represented different populations, 4 studies were from Asia (Japan), 10 from North America, 7 from Europe, and 1 was from Israel. Most studies had relevant controls for some conventional risk factors, including BMI (n = 13), smoking (n = 13), physical activity (n = 11), and dietary energy intake (n = 15). Some studies were also adjusted for alcohol use (n = 9) and other dietary variables or nutrients (n = 6). The quality scores of each study were summarized in Supplementary Table 1, http://links.lww.com/MD/A455. The quality scores ranged from 5 to 9, with the median score of 8. The majority of the included studies (18/22) were of high quality (NOS score ≥7).

Total Vegetables and Fruits Combined

High Versus Low Analysis

Eight studies investigated the association between the highest versus lowest intake of vegetables and fruits combined and CRA risk. The observed SRR of 0.82 (95% CI: 0.75–0.91) was observed, with no evidence of heterogeneity ($I^2 = 7.9\%$; Fig. 2A).

Dose–Response Analysis

Six studies were part of this dose–response analysis (Figure 2B). The SRR value per 100 g/d increment of fruits and vegetables combined was 0.99 (95% CI: 0.98–0.99), with no evidence of heterogeneity ($I^2 = 3.7\%$, $P_{\text{heterogeneity}} = 0.401$). Moreover, there was no evident nonlinear association between intake of vegetables and fruits combined and CRA risk ($P_{\text{nonlinearity}} = 0.101$; Supplementary Figure 1A, http://links.lww.com/MD/A455).

Total Vegetables

High Versus Low Analysis

Seventeen studies investigated the association between the highest versus lowest vegetables intake and CRA risk. The observed SRR was 0.91 (95% CI: 0.80–1.02), with moderate heterogeneity ($I^2 = 3.7\%$, $P_{\text{heterogeneity}} = 0.025$; Fig. 3A).

Dose–Response Analysis

Dose–response analysis was performed based on the data from 10 studies (Figure 3B). The SRR value per 100 g/d increment of vegetables was 0.98 (95% CI: 0.96–1.01), with evidence of high heterogeneity ($I^2 = 70.3\%$, $P_{\text{heterogeneity}} < 0.001$). In addition, there was a nonlinear association ($P_{\text{nonlinearity}} = 0.024$; Supplementary Figure 1B, http://links.lww.com/MD/A455).

Total Fruit

High Versus Low Analysis

Twenty studies representing the association between the highest versus lowest fruits intake and CRA risk were used for this analysis. The observed SRR was 0.79 (95% CI: 0.71–0.88), and there was a low heterogeneity ($I^2 = 27.0\%$; Fig. 4A).

Dose–Response Analysis

Dose–response analysis was achieved by including 12 studies (Figure 4B). The SRR value per 100 g/d increment of fruits was 0.94 (95% CI: 0.92–0.97), with low heterogeneity.

FIGURE 1. Flow diagram representing the systematic literature search on vegetables and fruits intake and CRA risk.
| Author/Year/ Country | No. of Cases, Age and Sex | No. of Controls | Examination in Controls | Dietary Assessments | Contrast (Highest vs Lowest) | RR (95% CI) | (Highest vs Lowest) | Adjustments |
|----------------------|--------------------------|----------------|------------------------|--------------------|-----------------------------|------------|---------------------|-------------|
| Macquart-Moulin/1987/France | 252 CRA | 238 general population | No endoscopy | Interviewed FFQ-140, NA | F: Q4 vs Q1 | 0.70 (0.37–1.32) | Age, sex |
| Benito/1993/Spain | 101 CRA, age: M + W | 242 general population | No endoscopy | Interviewed FFQ-99, NA | F: Q4 vs Q1 | 0.24 (0.11–0.54) | Age, sex |
| Kono/1993/Japan | 187 CAM, age: 63.5 (M), 62.2 (W) | 409 Polyp-free | Partial Self-administered FFQ, NA | Interview | F: 1d vs <4/ wk | 0.91 (0.63–1.31) | Age, alcohol intake, BMI, smoking, rank |
| Sandler/1993/the United States | 236 CRA, age: 63.5 (M), 62.2 (W) | 409 Polyp-free | Full Interview | Validated FFQ | F: 8 servings/wk | 0.44 (0.20–0.95) | W |
| Witte/1996/the United States | 529 CRA | 563 polyp-free | Partial Self-administered | | | | |
| Lubin/1997/Israel | 196 CRA, age: 63 (M) | 196 adenoma-free | Full Interview | Validated FFQ | F: 4.5 vs 9.0 servings/wk | 0.90 (0.49–1.68) | Age, sex, physical activity, total energy intake |
| Hoshiyama/2000/Japan | 105 CRA | 84 polyp-free | Full Self-administered | Validated FFQ | F: 2 servings/d vs <4 servings/wk | 1.69 (0.86–3.33) | Age, sex |
| Almendingen/2001/Japan | 87 CRA, age: 66 y, M + W | 35 polyp-free | Full 5-d dietary record | | | | |
| Broere-Katschinski/2001/German | 184 CRA | 178 polyp-free | Full Interview | Validated FFQ-126 | F: 5 vs Q1 | 0.65 (0.34–1.27) | Age, sex, energy, relative weight, and social class |
| Senesse/2002/France | 362 CRA | 427 polyp-free | Full Interview | Validated FFQ | F: Q4 vs Q1 | 0.9 (0.6–1.5) | LA |
| Smith-Warner/2002/the United States | 564 CRA | 535 polyp-free | Full Self-administered | Validated FFQ-153 | F: 7.5 vs 3.3 servings/wk | 1.34 (0.66–2.69) | W |
| Age: 58 | 682 community control | Validated FFQ-153 | | | | | |
| M + W | | | | | | |
| Author/Year/ | Country | No. of Cases | Age and Sex | No. of Controls | Examination | Dietary Assessments | Contrast (Highest vs Lowest) | RR (95% CI) | Adjustments |
|------------|---------|--------------|-------------|----------------|-------------|---------------------|-----------------------------|-------------|-------------|
| Chiu/2004/the United States | 146 CRA | 226 polyp-free | Partial | Self-administered | | V: Q5 vs Q1 | | 0.5 (0.2–1.1) | Age, sex, total energy intake, pack-years of smoking, physical activity, and use of NSAIDs |
| | | | | | Validated FFQ-100 | F: Q5 vs Q1 | | 0.7 (0.3–1.4) | |
| Wark/2006/The Netherlands | 534 CRA, | 709 polyp-free | Full | | Self-administered | V: ≥124.5 vs ≤91.9 g/d | | 1.27 (0.68–2.39) | Age, sex, total energy |
| | Age: 57, M + W | | | | | F: ≥230.8 vs ≤105.5 g/d | | 1.21 (0.65–2.26) | |
| Skjelbred/2007/Norway | 991 CRA | 400 polyp-free | Partial | Self-administered | | VF: >391 vs <166 g/d | | 1.03 (0.55–1.95) | Age, sex, smoking, alcohol consumption |
| | | | | | Validated FFQ | VF: >391 vs <166 g/d | | 0.99 (0.63–1.57) | NAA³ |
| Wu/2009/the United States | 764 CRA | 1517 polyp-free | Full | Interview | | VF: T3 vs T1 | | 0.94 (0.72–1.22) | |
| | | | | | Validated FFQ-108 | V: T3 vs T1 | | 0.94 (0.72–1.22) | |
| | | | | | | VF: T3 vs T1 | | 0.75 (0.58–0.97) | |
| Northwood/2010/United Kingdom | 317 CRA | 296 polyp-free | Full | Interview | | F: >103 vs <30 servings/mo | | 0.87 (0.55–1.38) | Age, sex and smoking |
| | | | | | | F: >103 vs <30 servings/mo | | 0.87 (0.55–1.38) | |
| | | | | | | V: >150 vs <73 servings/mo | | 0.35 (0.22–0.56) | |
| Yang/2014/the United States | 401 CRA | 518 polyp-free | Full | Self-administered | | VF: >250 vs <117 servings/mo | | 0.55 (0.34–0.88) | Age, sex, FHC, smoking, NSAID use |
| | | | | | Validated FFQ | VF: T3 vs T1 | | 1.24 (0.85–1.82) | |
| | | | | | | VF: T3 vs T1 | | 1.24 (0.85–1.82) | |

AA = advanced adenoma, BMI = body mass index, CI = confidence interval, CRA = colorectal adenoma, F = fruits, FFQ = food frequency questionnaire, FHC = family history of colorectal cancer, LA = large adenoma, NA = not available, NAA = nonadvanced adenoma, NSAIDs = nonsteroid anti-inflammatory drugs, SA = small adenoma, V = vegetable, VF = vegetable and fruits. ³ Nonadvanced adenoma: small (<1 cm), no high-grade dysplasia, and no villous elements. Advanced adenoma: large (≥1 cm), or with high-grade dysplasia, or with villous elements (including tubulovillous adenomas).
| Author/Year/Country | Number of Cases, Age and Sex | Number of Cases, Age and Sex | Dietary Assessments | Follow-Up, y | Contrast (Highest vs Lowest) | RR (95% CI) (Highest vs Lowest) | Adjustments |
|---------------------|-----------------------------|-----------------------------|---------------------|-------------|-----------------------------|---------------------------------|--------------|
| Platz/1997/the United States | N = 16,448 colonoscopy and/or sigmoidoscopy | 690 CRA | Self-administered | 8 | VF: 10.1 vs 3.0 servings/d | 0.82 (0.60–1.13) | Age, endoscopy, FHC, BMI, smoking, multivitamin use, physical activity, aspirin use, energy, alcohol, red meat, folate, and methionine. |
| Terakawa/2001/Japan | Takayama study 31,552 having a colonoscopy | 259 CRA | Self-administered | 2 | F: 3.4 vs 0.4 servings/d V: 6.3 vs 1.6 servings/d | 0.73 (0.54–1.00) | Age, total energy, smoking |
| Michel/2006/the United States | NHS: 34,467 females having a colonoscopy and/or sigmoidoscopy | n = 1720 CRA | Self-administered | 14 | F: ≥5 vs ≤1 servings/d | 0.60 (0.44–0.81) | Age, FHC, BMI, vigorous exercise, aspirin use, smoking, current multivitamin supplement use, alcohol consumption, total caloric intake, red meat consumption, calcium intake, menopausal status, and postmenopausal hormone use |
| Millen/2007/the United States | PLCO | n = 3057 CRA | Self-administered | NA | V: ≥5 vs ≤1 servings/d | 0.82 (0.65–1.05) |
| Tantamango/2011/the United States and Canada | AHS-1 and AHS-2 | 441 CRA | Self-administered | 26 | V: 7.3 vs 2.8 servings/d | 0.94 (0.83–1.06) | Age, sex, BMI |

AHS = Adventist Health Study, BMI = body mass index, CI = confidence interval, CRA = colorectal adenoma, FFQ = food frequency questionnaire, FHC = family history of colorectal cancer, HPFS = Professionals Follow-up Study, NA = not available, NHS = Nurses’ Health Study, NSAID = nonsteroid anti-inflammatory drugs, PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.
A FIGURE 2. Analysis of combined vegetables and fruits intake with risk of colorectal adenoma: (A) high versus low intake; (B) dose–response analyses for intake of 100 g/d increments.

(\(I^2 = 23.0\%\), \(P_{\text{heterogeneity}} = 0.205\)). There was no evident non-linear association between fruits intake and CRA risk (\(P_{\text{nonlinearity}} = 0.583\); Supplementary Figure 1C, http://links.lww.com/MD/A455).

Subgroup, Meta-Regression, and Sensitivity Analyses

In stratified analyses (Table 3), the association of high versus low intake of fruits and vegetables combined or separately with CRA risk suggested an inverse associations in studies conducted in Western countries, but not in the Asian countries. The stratified analysis based on sex demonstrated that intake of fruits had statistically significant associations for men (SRR = 0.81; 95% CI: 0.67–0.97), but not for women (SRR = 0.78; 95% CI: 0.49–1.24).

In meta-regression analyses (Table 3), the heterogeneity for association between fruits and vegetables was significant (\(P = 0.092\) and 0.071, respectively) based on the geographical locations. Furthermore, in the case of vegetables intake, confounders adjusted for smoking (\(P = 0.041\)) and total energy intake (\(P = 0.076\)) appeared to be the significant factors determining its association with CRA risk. Adjustments for smoking and total energy intake significantly attenuated the protective role of vegetables consumption.

We confirmed the stability of this inverse association by calculating the overall homogeneity and effect size by removing one study at a time (data not shown). Moreover, repeated analysis of high versus low intake using the studies included in the linear dose–response analysis for intake produced results that were similar to those of the original analysis (fruit and vegetables combined: SRR = 0.81; 95% CI: 0.74–0.89; vegetable: SRR = 0.87; 95% CI: 0.73–1.04; fruit: SRR = 0.80; 95% CI: 0.70–0.91).

Publication Bias

Egger test revealed the publication bias (\(P = 0.040\)) for intake of vegetables and fruits combined, whereas Begg test did not confirm this (\(P = 0.993\); Supplementary Figure 2A, http:// links.lww.com/MD/A456).

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risk of CRA in both case control and cohorts studies. There was a risk reduction by 21% in high versus low analysis, and 6% in 100 g/d increment of fruit consumption. To our knowledge, this is the first report suggesting a linear inverse association between intake of fruits and CRA risk.

Associations between intake of vegetables and fruits and CRA risk have been inconsistently reported among different observational studies. Some prospective studies have shown a reduced risk in subjects with high intake of fruits and vegetables combined or just fruits, but not with high consumption of vegetables. In contrast, some other studies observed opposite results. This disparity can be explained by several factors, including potential bias in each study, the definition and range of dietary intake, the limitations of currently available dietary assessment tools, and the potential confounders for which analyses were adjusted. Furthermore, randomized intervention trials on this topic also indicated that the adoption of diet higher in fruits and vegetables did not affect the recurrence of CRAs or rectal mucosal cell proliferation rates. The tentative biological explanation for this inconsistency can be correlated to the nutritional factors that affect critical events in colorectal carcinogenesis at molecular, cellular, or tissue level, well before polyps are formed. In addition, the clinical trials always included high-risk populations, whereas the observational studies examined average-risk populations. In addition, the clinical trials might be subjected to shorter follow-up periods and smaller quantities of consumption, and thus explain this discrepancy.

Our data on the associations between intake of vegetables and fruits together or alone and CRA suggested a significant inverse association among studies carried out in Western populations, but a null association was observed among Asian studies (Japan). These differences can be attributed not only by differences in genetic susceptibility, but also to the different types of vegetables and fruits consumed and types of methods used for production, storage conditions, nutrient content, and cooking/preparation in each study. In addition, the lower number of Asian studies (4 for fruit intake and 2 for vegetables intake) represented low statistical power and hence limited the overall results. Thus, more studies from Asian population are needed to demonstrate this association.

Based on the stratified analysis according to sex, we observed a significantly reduced CRA risk for men, but not for women in terms of fruit intake; however, consumption of vegetables did not show any associations in either sex. Although AA data were very informative with regard to the preventive strategies of CRC, we could not study this association because of the unavailability of sufficient data. Millen et al have reported that intake of fruits, but not vegetables, was associated with reduced risk for both NAA and AA. Another report from Skjelbred et al observed a null association of both NAA and AA with combined intake of vegetables and fruits. Similarly, insufficient data were available for colon and rectal adenoma. Millen et al have shown that intake of fruits was associated with reduced risk of colon adenoma (OR = 0.70, 95% CI: 0.60–0.82), but not rectal adenoma (OR = 0.89, 95% CI: 0.68–1.16). In contrast, a case-control study by Kono et al examined no association between fruits intake and colon adenoma risk. Another study presented results for single and multiple (≥2) adenomas, and found that increased intake of fruits, but not vegetables, was significantly related to the decreased risk of single and multiple (≥2) adenomas. These results, thus, should be interpreted with caution because the current analysis was

### DISCUSSION

The overall results of this meta-analysis suggested that intake of fruits was associated with significant reductions in the risk of CRA.
| Subgroups | n | SRR (95% CI) | $P_{h,I}$ ($\chi^2$) | $P_d$ | n | SRR (95% CI) | $P_{h,I}$ ($\chi^2$) | $P_d$ | n | SRR (95% CI) | $P_{h,I}$ ($\chi^2$) | $P_d$ |
|-----------|---|-------------|---------------------|------|---|-------------|---------------------|------|---|-------------|---------------------|------|
| All       | 8 | 0.82 (0.75–0.91) | 0.369, 7.9 | 17  | 0.91 (0.80–1.02) | 0.025, 41.5 | 20  | 0.79 (0.71–0.88) | 0.111, 27.0 |
| Design    |   |             |                      |      |               |                      |      |               |                      |      |
| Case-control | 5 | 0.85 (0.68–1.06) | 0.139, 38.0 | 12  | 0.86 (0.71–1.05) | 0.053, 40.4 | 15  | 0.78 (0.67–0.92) | 0.135, 27.5 | 0.925 |
| Cohort    | 3 | 0.82 (0.74–0.90) | 0.993, 0 | 5   | 0.95 (0.81–1.10) | 0.079, 49.3 | 5   | 0.79 (0.68–0.92) | 0.154, 37.8 |
| Locations |   |             |                      |      |               |                      |      |               |                      |      |
| Western   | 8 | 0.82 (0.75–0.91) | 0.369, 0 | 14  | 0.87 (0.76–0.99) | 0.034, 42.3 | 15  | 0.75 (0.66–0.84) | 0.132, 27.8 | 0.092 |
| Asia (Japan) | – | – | – | – | 2 | 1.29 (0.94–1.76) | 0.511, 0 | 4   | 0.95 (0.76–1.19) | 0.625, 0 |
| Sex       |   |             |                      |      |               |                      |      |               |                      |      |
| Male      | 2 | 0.78 (0.58–1.04) | 0.442, 0.772 | 4   | 1.08 (0.87–1.34) | 0.920, 0.536 | 5   | 0.81 (0.67–0.97) | 0.716, 0.882 |
| Female    | 2 | 0.82 (0.69–0.97) | 0.650, 0 | 4   | 0.88 (0.48–1.63) | 0.033, 65.6 | 4   | 0.78 (0.49–1.24) | 0.043, 63.1 |
| Type of FFQ |   |             |                      |      |               |                      |      |               |                      |      |
| Validated | 8 | 0.82 (0.75–0.91) | 0.369, 0 | 15  | 0.92 (0.80–1.05) | 0.014, 46.4 | 16  | 0.79 (0.72–0.88) | 0.271, 14.7 | 0.479 |
| Nonvalidated | – | – | – | – | 2 | 0.77 (0.50–1.19) | 0.922, 0 | 4   | 0.61 (0.35–1.06) | 0.031, 66.3 |
| Exposure data |   |             |                      |      |               |                      |      |               |                      |      |
| Self-administered | 6 | 0.84 (0.77–0.92) | 0.516, 0.167 | 9   | 0.96 (0.84–1.10) | 0.102, 37.2 | 11  | 0.72 (0.56–0.90) | 0.080, 40.4 |
| Interview administered | 2 | 0.69 (0.52–0.90) | 0.260, 20.9 | 8   | 0.80 (0.63–1.02) | 0.066, 44.0 | 11  | 0.72 (0.56–0.90) | 0.080, 40.4 |
| <360      |   |             |                      |      |               |                      |      |               |                      |      |
| ≥360  | 8 | 0.82 (0.75–0.91) | 0.369, 0 | 9   | 0.92 (0.85–1.00) | 0.001, 81.7 | 9   | 0.78 (0.69–0.87) | 0.234, 22.0 |
| Study quality score |   |             |                      |      |               |                      |      |               |                      |      |
| High (NOS score >6) | 8 | 0.82 (0.75–0.91) | 0.369, 0 | 14  | 0.91 (0.79–1.04) | 0.013, 47.7 | 16  | 0.80 (0.71–0.85) | 0.374, 6.6 | 0.958 |
| Low (NOS score ≤6) | – | – | – | – | 3 | 0.91 (0.63–1.29) | 0.438, 0 | 4   | 0.70 (0.40–1.22) | 0.011, 12 |
| Endoscopy in controls |   |             |                      |      |               |                      |      |               |                      |      |
| Full      | 4 | 0.80 (0.59–1.08) | 0.073, 53.3 | 0.810 | 9 | 0.98 (0.78–1.23) | 0.007, 56.0 | 0.366 | 11 | 0.83 (0.72–0.96) | 0.336, 10.5 | 0.370 |
| Partial/full + partial | 4 | 0.83 (0.75–0.91) | 0.889, 0 | 0.8 | 0.89 (0.81–0.97) | 0.511, 0 | 9 | 0.74 (0.63–0.88) | 0.062, 46.2 |
| Adjustments |   |             |                      |      |               |                      |      |               |                      |      |
| BMI, yes  | 6 | 0.82 (0.75–0.89) | 0.925, 0.572 | 10  | 0.92 (0.85–0.99) | 0.747, 0.528 | 12  | 0.76 (0.69–0.85) | 0.272, 16.2 | 0.338 |
| No        | 2 | 0.84 (0.38–1.86) | 0.009, 85.4 | 7 | 0.84 (0.58–1.23) | 0.001, 72.7 | 8 | 0.83 (0.64–1.07) | 0.097, 40.6 |
| Smoking, yes | 7 | 0.83 (0.77–0.91) | 0.544, 0.130 | 10 | 0.96 (0.88–1.05) | 0.419, 0.041 | 11 | 0.77 (0.70–0.85) | 0.362, 8.3 | 0.599 |
| No        | 1 | 0.55 (0.34–0.89) | – | 7 | 0.76 (0.58–0.99) | 0.043, 51.8 | 9 | 0.75 (0.57–0.98) | 0.05, 46.8 |
| Energy intake, yes | 5 | 0.81 (0.72–0.92) | 0.866, 0.807 | 13 | 0.94 (0.85–1.05) | 0.386, 5.8 | 0.076 | 14 | 0.81 (0.71–0.92) | 0.201, 21.2 | 0.518 |
| No        | 3 | 0.84 (0.59–1.19) | 0.028, 72.1 | 4 | 0.67 (0.41–1.10) | 0.001, 81.7 | 6 | 0.73 (0.57–0.93) | 0.094, 46.8 |
| Physical activity, yes | 6 | 0.82 (0.75–0.89) | 0.925, 0.572 | 10 | 0.91 (0.84–0.99) | 0.557, 0.839 | 10 | 0.77 (0.69–0.85) | 0.340, 10.7 | 0.587 |
| No        | 2 | 0.84 (0.38–1.86) | 0.009, 85.4 | 7 | 0.90 (0.62–1.31) | 0.002, 67.1 | 10 | 0.79 (0.62–0.99) | 0.068, 40.9 |

BMI = body mass index, CI = confidence interval, FFQ = food frequency questionnaire, NOS = Newcastle-Ottawa Quality Assessment Scale, SRR = summary relative risk.
based on only very few studies. Hence, more studies with sufficient number of data points based on sex, histopathology (nonadvanced or advanced), or location (colon or rectum) are required for a comprehensive analysis about this association.

We observed inverse association between CRA risk and intake of fruits, but not vegetables, and it can be explained through several potential mechanisms. Although both the fruits and vegetables are good sources of various antioxidants, vitamins, dietary fiber, folate, and flavonoids, there were different effects of these constituents on colorectal carcinogenesis. For example, our previous meta-analysis\textsuperscript{45} and other prospective cohort studies\textsuperscript{46,47} have suggested that increased dietary fiber intake may lead to decreased risk of colorectal neoplasm. Furthermore, a statistically significant inverse association was observed between CRA and fiber from fruits and cereals, but not from vegetables.\textsuperscript{45}

Furthermore, our study has several strengths. The combined sample size was large and included several prospective cohort studies. CRA outcomes in all studies were ascertained using endoscopy and pathohistological findings. In most of the studies, the risk estimates from the fully adjusted models were used for analyses to reduce the potential of confounding. The dose–response analysis was conducted to evaluate the linear and nonlinear relations, which helps to quantify and test the shape of these associations. We performed several sensitivity analysis based on sex, geographic locations, study quality score, exposure assessment, and important confounding factors.

However, there were also several limitations of this meta-analysis. First was the problem of measurement errors in the assessment of dietary intake. To cover this aspect, we included studies evaluating all fruits or vegetables, but there were differences in their classifications and types consumed in studies from different regions, ethnicities, and time periods. All these had the potential to affect our results. Indeed, our subgroup analyses showed that the associations between consumption of fruits and vegetables with CRA risk differ significantly by study location. Most of the included studies (18/22) used a validated FFQ to evaluate the consumption of fruit and vegetables. However, subgroup analysis suggested that the use of a validated or unvalidated FFQ did not significantly change our findings.

To summarize, the current meta-analysis supported the hypothesis that a high intake of fruits, but not vegetables, was inversely associated with CRA risk. Further studies with prospective designs, that use validated questionnaires and controls for important confounders, would be required to verify our findings.

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