

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

A PRISMA-Compliant Meta-Analysis of Observational Studies

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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, $P_{\text{heterogeneity}} = 0.025$), whereas for vegetables and fruits combined, it was 0.82 (95% CI: 0.75–0.91, $P_{\text{heterogeneity}} = 0.369$), and for fruits alone, it was 0.79 (95% CI: 0.71–0.88, $P_{\text{heterogeneity}} = 0.111$). 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 ($P_{\text{nonlinearity}} = 0.024$), but not for fruits ($P_{\text{nonlinearity}} = 0.583$).

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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QB and JZ contributed equally to this manuscript.

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Abbreviations: BMI = body mass index, CRA = colorectal adenoma, CRC = colorectal cancer, FFQ = food frequency questionnaires, NAA/AA = nonadvanced/advanced adenoma, NOS = Newcastle-Ottawa Quality Assessment Scale.

INTRODUCTION

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer and the second leading cause of cancer deaths in the United States.¹ Several environmental risk factors, such as smoking, obesity, physical inactivity, and some dietary factors, have been identified to contribute to the etiology of the CRC. The 40% of the population by the age of 60 years develop colorectal adenomas (CRAs), which are precursor lesions of CRC. CRA is an informative and important endpoint for colon carcinogenesis because it shares common etiopathogenesis with CRC. However, other than the age factor, smoking,² obesity,³ and physical inactivity,⁴ very little is known about additional factors that contribute in the development of CRA.

Consumption of vegetables and fruits has generated interest for a long time because of their beneficial role in the prevention of cancers, including CRC. The different mechanisms that have been suggested for prevention of cancer includes modulation of DNA methylation, protection from DNA damage, promotion of apoptosis, and induction of detoxifying phase-II enzymes.⁵ Previous report of 2007 has provided some evidence for the associations between nonstarchy vegetables and fruits consumption with CRC development.⁶ However, these evidences were not very convincing and were more of suggestive nature only. Moreover, the Continuous Update Project Report in 2011 from the World Cancer Research Fund/American Institute for Cancer Research also did not alter these conclusions.⁷

In addition, epidemiological studies^{8–29} have also reported inconsistent results regarding the association between intake of vegetables and fruits with CRA risk. For example, data from the Nurse's Health Study²² and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial²⁴ concluded that the prevalence of CRA is decreased by intake of fruit only but not vegetables. In contrast, the Adventist Health Study linked the decreased risk of CRAs with only consumption of vegetables and not fruits.²⁸ In addition, number of other studies have shown a nonsignificant risk associations.^{8–10,12,14,20,21} To our knowledge, there has been no comprehensive quantitative assessment of the risk association of vegetables and fruits consumption with CRA, and therefore we undertook this study to shed some more light on the role of fruits and vegetables consumption on CRA.

METHODS

We preformed the meta-analysis to assess the association between consumption of vegetables and fruits with CRA

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 number of potential confounders. Studies that reported both hospital- and population-based controls, only the risk estimations from the hospital-based controls were considered since they had an endoscopy.

Quality Assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS)³¹ was used to assess the quality of each selected study. Based on

the NOS, a study can be assigned a score of total 9 points (9 representing the highest quality) following these criteria: 4 points for selection, 2 points for comparability, and 3 points for exposure/outcome assessment. A total score ≥ 7 indicated high quality study. To avoid selection bias, no study was rejected because of these quality criteria.

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 non-linear 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 I^2 statistics. P value of <0.10 represented statistically significant heterogeneity. I^2 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 analysis^{34,35} 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

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

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 SRR of 0.82 (95% CI: 0.75–0.91) was observed, with no evidence of heterogeneity ($P_{\text{heterogeneity}} = 0.369$, $I^2 = 7.9\%$; 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 ($P_{\text{heterogeneity}} = 0.025$, $I^2 = 41.5\%$; 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 ($P_{\text{heterogeneity}} = 0.111$, $I^2 = 27.0\%$; 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

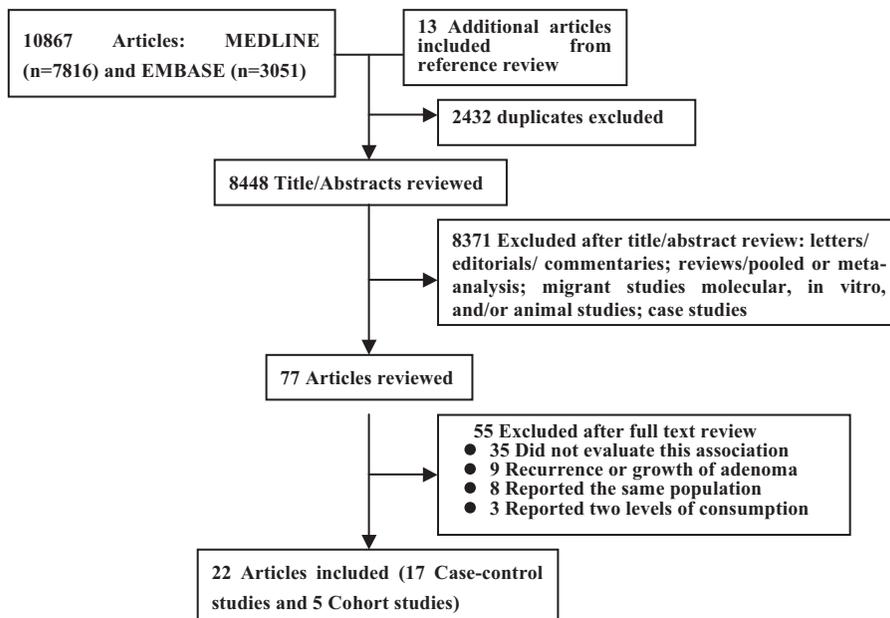


FIGURE 1. Flow diagram representing the systematic literature search on vegetables and fruits intake and CRA risk.

TABLE 1. Characteristics of Case-Control Studies Involving Vegetables and Fruits Intake With Colorectal Adenoma 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 Age: 59 (M), 62 (W)	238 general population	No endoscopy	Interviewed FFQ-140, NA	F: Q4 vs Q1 V: Q4 vs Q1	0.70 (0.37–1.32) 0.78 (0.48–1.27)	Age, sex
Benito/1993/Spain	101 CRA M + W	242 general population	No endoscopy	Interviewed FFQ-99, NA	F: Q4 vs Q1 V: Q4 vs Q1	0.24 (0.11–0.54) 0.74 (0.29–1.90)	Age, sex
Kono/1993/Japan Sandler/1993/the United States	187 CAM 236 CRA, age: 63.5 (M), 62.2 (W)	1557 polyp-free 409	Partial Full	Self-administered FFQ, NA Interview	F: 1/d vs <4/wk F: ≥22.3 vs <8.4 servings/wk V: ≥24.8 vs <11.2 servings/wk F: ≥19.9 vs <6.3 servings/wk V: ≥23.9 vs <11.1 servings/wk	0.91 (0.63–1.31) 0.44 (0.20–0.95) W 0.74 (0.35–1.57) W 0.60 (0.24–1.52) M 1.20 (0.49–2.93) M	Age, alcohol intake, BMI, smoking, rank Age, alcohol intake, BMI, and calories
Witte/1996/the United States	529 CRA	563 polyp-free	Partial	Self-administered	F: 25.0 vs 2.5 servings/wk	0.92 (0.52–1.63)	Age, race, BMI, physical activity, smoking, calories, and saturated fat dietary fiber, folate, beta- carotene, and vitamin C
Lubin/1997/Israel	Age: 61.9 M + W 196 CRA, age: 63 (M) 60 (W)	196 adenoma-free	Full	Validated FFQ Interview	V: 45.5 vs 9.0 servings/wk V: T3 vs T1	0.90 (0.49–1.68) 0.9 (0.6–1.6)	Age, sex, physical activity, total energy intake
Hoshiyama/2000/ Japan	105 CRA Age: 40–69 M + W	84 polyp-free	Full	FFQ-180 Validated Self-administered FFQ	F: T3 vs T1 F: ≥2 servings/d vs <4 servings/wk	1.1 (0.6–1.9) 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	F: ≥321 vs ≤110 g/d V: ≥181 vs ≤80 g/d	2.9 (0.6–14.5) 1.1 (0.2–5.1)	Age, sex, BMI, tobacco use, energy, fat, fiber, and FHC
Breuer-Katschinski/ 2001/German	184 CRA Age: 63.8, M + W 362 CRA	178 polyp-free 182 general population	Full	Interview Validated FFQ-126	F: Q5 vs Q1 V: Q4 vs Q1 V: Q4 vs Q1	0.65 (0.34–1.27) 1.1 (0.6–1.9) SA 0.9 (0.6–1.5) LA	Age, sex, energy, relative weight, and social class
Senesse/2002/France	Age: 59.5, M + W	427 polyp-free	Full	Validated FFQ	F: Q4 vs Q1	1.0 (0.6–1.7) SA 0.75 (0.55–1.2) LA	Age, sex, energy intake, BMI, alcohol, and tobacco
Smith-Warner/2002/ the United States	564 CRA Age: 58 M + W	535 polyp-free 682 community control	Full	Self-administered Validated FFQ-153	F: 27.5 vs. 3.3 servings/wk F: 26.9 vs 2.1 servings/wk V: 51.4 vs 10.1 servings/wk V: 44.7 vs 8.8 servings/wk VF: 82.8 vs 18.4 servings/wk VF: 75.9 vs 16.5 servings/wk	1.34 (0.66–2.69) W 0.66 (0.35–1.24) M 1.70 (0.87–3.34) W 0.90 (0.48–1.69) M 0.96 (0.47–1.96) W 0.61 (0.31–1.22) M	Age, energy intake, fat intake, BMI, smoking status, alcohol status, NSAID, multivitamin use, and hormone replacement therapy use

Chiu/2004/the United States	146 CRA Age: 58 M + W	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
Wark/2006/The Netherlands	534 CRA, Age: 57, M + W	709 polyp-free	Full	Validated FFQ-100 Self-administered	F: Q5 vs Q1 V: ≥128.5 vs ≤91.9 g/d	0.7 (0.3–1.4) 1.27 (0.68–2.39)	Age, sex, total energy
Skjelbred/2007/Norway	991 CRA Age: 53 M + W	400 polyp-free	Partial	Validated FFQ-178 Self-administered	F: ≥230.8 vs ≤105.5 g/d VF: >391 vs <166 g/d	1.21 (0.65–2.26) 1.03 (0.55–1.95)/AA ¹	Age, sex, smoking, alcohol consumption
Wu/2009/the United States	764 CRA	1517 polyp-free	Full	Validated FFQ Interview	VF: >391 vs <166 g/d F: T3 vs T1	0.99 (0.63–1.57) NAA ¹ 0.66 (0.51–0.86)	Age, sex, race, study location, BMI, smoking status, alcohol, NSAID use, physical exercise, education level, family income, FHC, red/processed meat, total energy intake
Northwood/2010/United Kingdom	Age: 59.6 M + W 317 CRA	296 polyp-free	Full	Validated FFQ-108 Interview	V: T3 vs T1 VF: T3 vs T1 F: >103 vs <30 servings/mo	0.94 (0.72–1.22) 0.75 (0.58–0.97) 0.87 (0.55–1.38)	Age, sex and smoking
Yang/2014/the United States	Age: 50–69, M + W 401 CRA Age: 58.3 M+W	518 polyp-free	Full	Validated FFQ Self-administered Validated FFQ-153	V: >150 vs <73 servings/mo VF: >250 vs <117 servings/mo VF: T3 vs T1	0.35 (0.22–0.56) 0.55 (0.34–0.88) 1.24 (0.85–1.82)	Age, sex, FHC, smoking, NSAID use

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, 1, 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).

TABLE 2. Characteristics of Cohort Studies Investigating the Effect of Vegetables and Fruits Intake on Colorectal Adenoma Risk

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.
Nagata/2001/Japan	Takayama study 31,552 having a colonoscopy	Age: 40–75 M 259 CRA	Validated FFQ-131 Self-administered	2	F: 3.4 vs 0.4 servings/d V: 6.3 vs 1.6 servings/d F: T3 vs T1	0.73 (0.54–1.00) 1.06 (0.78–1.44) 0.92 (0.64–1.32) M	Age, total energy, smoking
Michiel/2006/the United States	NHS: 34,467 females having a colonoscopy and/or sigmoidoscopy	Age: >35 M + W n = 1720 CRAW	Validated FFQ-169 Self-administered	14	F: T3 vs T1 V: T3 vs T1 V: T3 vs T1 F: ≥5 vs ≤1 servings/d	1.11 (0.63–1.96) W 1.15 (0.79–1.69) M 1.73 (0.98–3.18) W 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	Age: about 55 n = 3057 CRA	Validated FFQ-136 Self-administered	NA	V: ≥5 vs ≤1 servings/d VF: ≥7 vs ≤3 servings/d F: 5.7 vs 1.2 servings/d	0.82 (0.65–1.05) 0.81 (0.68–0.96) 0.75 (0.66–0.86)	Age, sex, study center, race, education, FHC, smoking, alcohol use, use of ibuprofen, use of aspirin, use of replacement hormones, physical activity, BMI
Tantamango/2011/ the United States and Canada	N = 44,532 sigmoidoscopy AHS-1 and AHS-2	Age: 55–74 M + W 441 CRA N = 2818	Validated FFQ-137 Self-administered	26	V: 7.3 vs 2.8 servings/d VF: 12.2 vs 4.7 servings/d V: T3 vs T1	0.94 (0.83–1.06) 0.82 (0.72–0.93) 0.76 (0.60–0.98)	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.

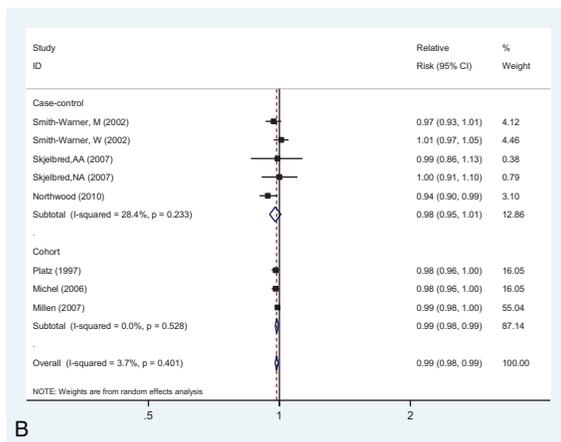
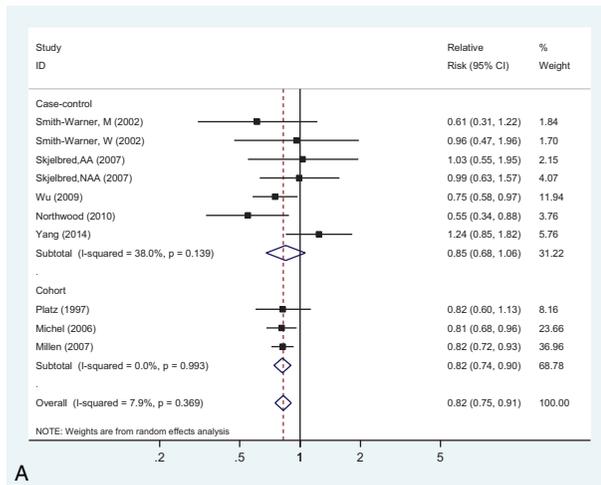


FIGURE 2. Analysis of combined vegetables and fruits intake with risk of colorectal adenoma: (A) high versus low analysis; (B) dose-response analyses for intake of 100 g/d increments.

($I^2 = 23.0\%$, $P_{\text{heterogeneity}} = 0.205$). 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 Analysis

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 for difference = 0.092 and 0.071, respectively) based on the geographical locations. Furthermore, in the case of vegetables intake, confounders adjusted for smoking (P for difference = 0.041) and total energy intake (P for difference = 0.076) appeared to be the

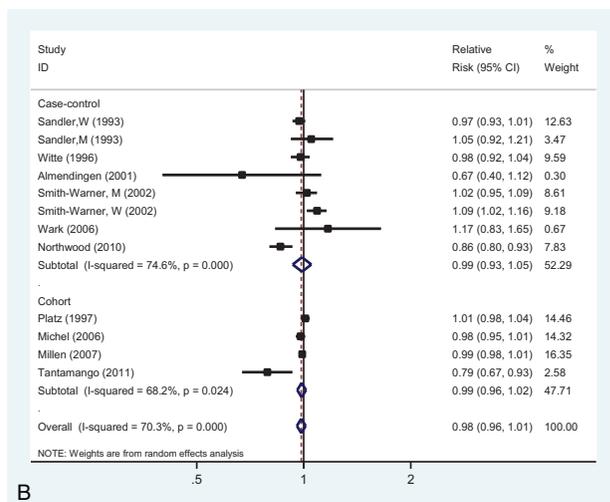
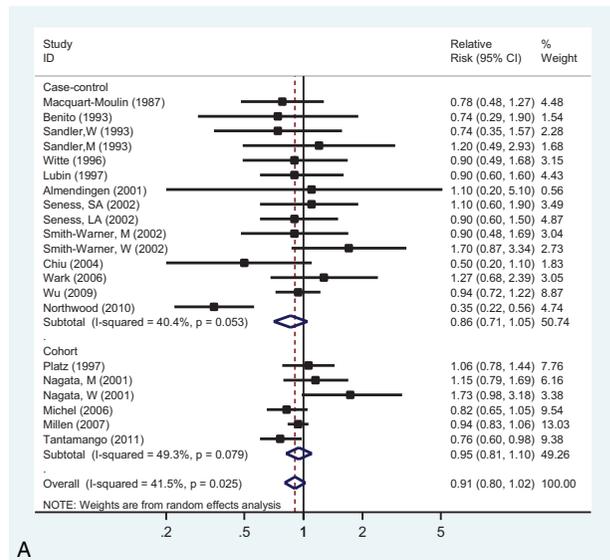


FIGURE 3. Analysis of vegetables intake with risk of colorectal adenoma: (A) high versus low intake; (B) dose-response analyses for intake of 100 g/d increment.

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://>

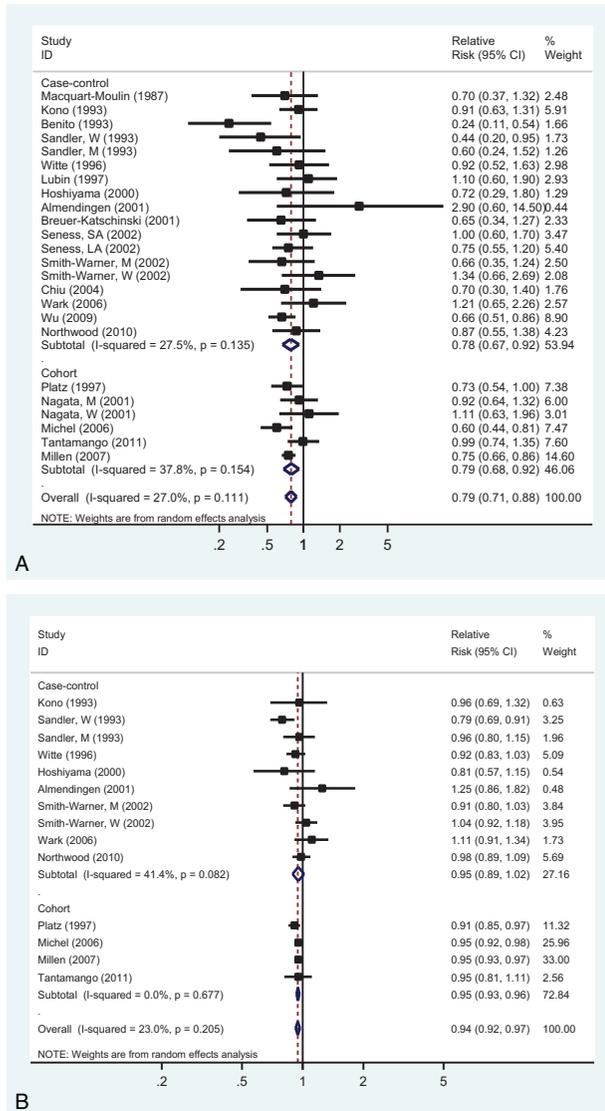


FIGURE 4. Analysis of fruits intake with risk of colorectal adenoma: (A) high versus low intake; (B) dose-response analyses for intake of 100 g/d increment.

links.lww.com/MD/A455). The trim-and-fill method suggested that no additional risk estimate was required to balance the funnel plot. In case of vegetables intake, there was no indication of publication bias by both Egger test ($P = 0.278$) and Begg test ($P = 0.740$; Supplementary Figure 2B, <http://links.lww.com/MD/A455>). But for fruit intake, Egger test revealed evidence of publication bias ($P = 0.003$), but Begg test did not ($P = 0.941$; Supplementary Figure 2C, <http://links.lww.com/MD/A455>). Moreover, the trim-and-fill method indicated that 2 additional risk estimates were needed to balance the funnel plot, and the summary risk estimates were similar (SRR = 0.78; 95% CI: 0.69–0.87).

DISCUSSION

The overall results of this meta-analysis suggested that intake of fruits was associated with significant reductions in the

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^{22–26} 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^{27,28} 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^{40–42} or rectal mucosal cell proliferation rates.⁴³ 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.⁴⁰ In addition, the clinical trials always included high-risk populations (ie, subjects with histories of adenoma), 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 CRA⁴⁴ 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 to the differences in genetic susceptibility, but also to the different types of fruits and vegetables 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 al²⁴ have reported that intake of fruits, but not vegetables, was associated with reduced risk for both NAA and AA. Another report from Skjelbred et al²⁵ 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 al²⁴ 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 al¹⁰ detected no association between fruits intake and colon adenoma risk. Another study²⁴ 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

TABLE 3. Stratified Meta-Analyses of Vegetables and Fruits Intake and Colorectal Adenoma Risk: High Versus Low Analysis

Subgroups	Vegetables and Fruits				Vegetables				Fruits			
	n	SRR (95% CI)	P_{het} , I^2 (%)	P_d	n	SRR (95% CI)	P_{het} , I^2 (%)	P_d	n	SRR (95% CI)	P_{het} , I^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	0.803	12	0.86 (0.71–1.05)	0.053, 40.4	0.405	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	0.071	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	0.772	4	1.08 (0.87–1.34)	0.920, 0	0.536	5	0.81 (0.67–0.97)	0.716, 0	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	0.548	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	0.167	9	0.96 (0.84–1.10)	0.102, 37.2	0.176	9	0.81 (0.73–0.90)	0.339, 10.6	0.283
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	–
No. of cases												
<360	–	–	–	–	8	0.83 (0.59–1.15)	0.004, 63.1	0.361	11	0.78 (0.63–0.97)	0.108, 34.3	0.697
≥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	0.981	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, 73.0	–
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	–	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	0.572	10	0.92 (0.85–0.99)	0.747, 0	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	0.130	10	0.96 (0.88–1.05)	0.419, 2.7	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	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	0.572	10	0.91 (0.84–0.99)	0.557, 0	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-analysis⁴⁵ and other prospective cohort studies^{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.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 the risk associations. It is very difficult for persons to accurately report their intake of vegetables or fruits, reflecting the relatively low correlation in validated studies (Spearman correlation coefficients of 0.6 for fruits consumption and 0.4 for vegetables consumption as demonstrated in previous studies).^{48,49} Measurement errors can also occur when intake levels are calculated based on different units. These measurement errors can lead to the attenuation of risk estimates and the true associations might be stronger than we observed,^{50,51} and thus strengthening our conclusion of protective effects of fruits on CRA risk.

In addition, there is a possibility of skewing the risk estimates toward null, if there is a misclassification of certain controls because of high rates of incomplete colonoscopies. However, stratified analyses based on type of endoscope in controls observed a similar summary risk estimates for studies with complete versus incomplete colonoscopies.

Second, unmeasured or uncontrolled confounders inherited from observational studies were another concern. Higher intakes of fruits and vegetables may be a marker for generally “healthier” dietary and lifestyle patterns such as a lower prevalence of tobacco smoking and overweight/obesity, drinking less alcohol, and being physically active.^{52,53} In addition, adjustment for total energy intake was important to account for

the potential confounding factors because of dietary correlates in nutritional studies.⁵⁴ Importantly, stratification based on adjustment for smoking status and total energy intake did significantly change the risk associations for vegetables intake. These results indicated that smoking status and total energy intake may have a residual confounding effect on the association between consumption of vegetables and adenoma risk. Smoking causes oxidative stress and DNA damage in the body, and active smokers have lower blood concentrations of ascorbic acid, alpha-carotene, beta-carotene, which explains why smokers benefit more from consumption of vegetables and fruits.⁵⁵

Third, moderate heterogeneity was observed among different studies, which can be attributed to the study design, geographic locations, number of cases, method of exposure measurement (eg, self- vs interviewer-administered questionnaires, type of FFQ), classification of vegetables, and fruits intake and adjustment for confounders. Indeed, the subgroup meta-analysis based on geographic locations showed that Asian studies had little variability, whereas significant heterogeneity was observed among Western studies on vegetables intake. Moreover, analyses of high versus low intake were limited because they did not account for true differences among studies at the level and range of intake, thus contributing to the heterogeneity between the results. But when we repeated the high versus low analyses with the same studies that were included in the dose–response analysis, results were not changed.

Finally, publication bias was also a concern because small studies with null results tend to be less published. Egger test did provide evidence of such bias; however, the results obtained from funnel plot and Begg tests did not provide evidence for publication bias. Furthermore, the trim-and-fill method showed that 2 additional risk estimates were required to balance the funnel plot for studies on fruits consumption, whereas the SRRs remained unchanged.

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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