

Nonlinear Reduction in Risk for Colorectal Cancer by Fruit and Vegetable Intake Based on Meta-analysis of Prospective Studies

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BACKGROUND & AIMS: The association between fruit and vegetable intake and colorectal cancer risk has been investigated by many studies but is controversial because of inconsistent results and weak observed associations. We summarized the evidence from cohort studies in categorical, linear, and nonlinear, dose–response meta-analyses. **METHODS:** We searched PubMed for studies of fruit and vegetable intake and colorectal cancer risk that were published until the end of May 2010. We included 19 prospective studies that reported relative risk estimates and 95% confidence intervals (CIs) of colorectal cancer-associated with fruit and vegetable intake. Random effects models were used to estimate summary relative risks. **RESULTS:** The summary relative risk for the highest vs the lowest intake was 0.92 (95% CI: 0.86–0.99) for fruit and vegetables combined, 0.90 (95% CI: 0.83–0.98) for fruit, and 0.91 (95% CI: 0.86–0.96) for vegetables (P for heterogeneity = .24, .05, and .54, respectively). The inverse associations appeared to be restricted to colon cancer. In linear dose–response analysis, only intake of vegetables was significantly associated with colorectal cancer risk (summary relative risk = 0.98; 95% CI: 0.97–0.99), per 100 g/d. However, significant inverse associations emerged in nonlinear models for fruits ($P_{\text{nonlinearity}} < .001$) and vegetables ($P_{\text{nonlinearity}} = .001$). The greatest risk reduction was observed when intake increased from very low levels of intake. There was generally little evidence of heterogeneity in the analyses and there was no evidence of small-study bias. **CONCLUSIONS: Based on meta-analysis of prospective studies, there is a weak but statistically significant nonlinear inverse association between fruit and vegetable intake and colorectal cancer risk.**

Keywords: Diet; Statistical Analysis; Tumor Prevention; Epidemiology.

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by which fruit and vegetables could reduce colorectal cancer risk,^{2,3} but epidemiological studies have provided inconsistent results. The first report from the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) in 1997 concluded that there was convincing evidence that vegetable intake, but not fruit intake, protects against colorectal cancer, based on a narrative review of the results from 22 case-control studies and 4 cohort studies.⁴ In contrast, most^{5–20} but not all^{21,22} prospective cohort studies published in the 10 subsequent years found no statistically significant associations between fruit and/or vegetable intakes and colorectal cancer risk. In line with this, several reviews and meta-analyses and a pooled analysis did not find statistically significant inverse associations between fruit and vegetable intakes and colorectal cancer risk in cohort studies.^{23–26} Although case-control studies continue to show strong evidence of an inverse association,^{23,24} these studies are more liable to recall and selection biases that can hamper the interpretation of their results.

In addition, the second report from the WCRF/AICR published in 2007, *Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective*, stated that there was limited suggestive evidence for risk reduction by fruits and nonstarchy vegetables, based on quantitative systematic reviews and meta-analyses of cohort studies, so a downgrading of the judgment of the evidence compared with the previous report.²⁷ However, although it has been hypothesized that very low intakes of fruits and vegetables can increase colorectal cancer risk,^{13,28} none of the previous meta-analyses have examined the shape of the dose–response relationship (ie, whether there are any threshold effects) by conducting nonlinear dose–response analyses.^{23,24,26,27} Results from 5 large prospective cohort studies have been published since the second WCRF/AICR report^{28–33} and here we update the evidence published up to May 2010 with an aim to clarify whether there is a nonlinear dose–response relationship between fruit and vegetable intakes and colorectal cancer risk.

Abbreviations used in this paper: AICR, American Institute for Cancer Research; CI, confidence interval; RR, relative risk; WCRF, World Cancer Research Fund.

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Intake of fruit and vegetables has been hypothesized to protect against several cancers, including colorectal cancer.¹ Experimental animal studies and human feeding studies have provided biologically plausible mechanisms

Materials and Methods

Search Strategy

We updated the systematic literature review published in 2007²⁷ and searched the PubMed database up to May 2010 for cohort studies of fruit and vegetable intake and colorectal cancer risk. We followed a prespecified protocol, which includes details of the search terms used, for the review (http://www.dietandcancerreport.org/downloads/SLR_Manual.pdf). We also searched the reference lists of all the studies that were included in the analysis and the reference lists of the published systematic reviews and meta-analyses.^{23,24,26,27} We followed standard criteria for conducting and reporting meta-analyses.³⁴

Study Selection

To be included, the study had to have a prospective cohort, case-cohort or nested case-control design and to investigate the association between the intake of fruit and vegetables and colorectal cancer incidence. Estimates of the relative risk (RR) (such as hazard ratio or risk ratio) and 95% confidence intervals (CIs) had to be available in the publication. For the dose-response analysis, a quantitative measure of intake and the total number of cases and person-years had to be available in the publication.

When multiple publications from the same study were available, we used the publication with the largest number of cases and sufficient information to be incorporated in the dose-response analyses. We excluded studies on colorectal cancer mortality, studies that did not provide risk estimates, duplicate publications, and for the dose-response analyses we excluded studies that did not report quantities or that only provided a comparison of the highest vs the lowest level of intake (Figure 1, Supplementary Appendix 1).

Data Extraction

We extracted the following data from each study: first author's last name, publication year, country where the study was conducted, study name, follow-up period, sample size, sex, age, number of cases, dietary assessment method (ie, type, number of items, and whether it was validated), exposure, frequency or quantity of intake, RRs and 95% CIs and variables adjusted for in the analysis. The search and data extraction of articles published up to June 2006 was conducted by several reviewers at Wageningen University during the systematic literature review for the WCRF/AICR report (http://www.dietandcancerreport.org/downloads/SLR/Colon_and_Rectum_SLR.pdf). The

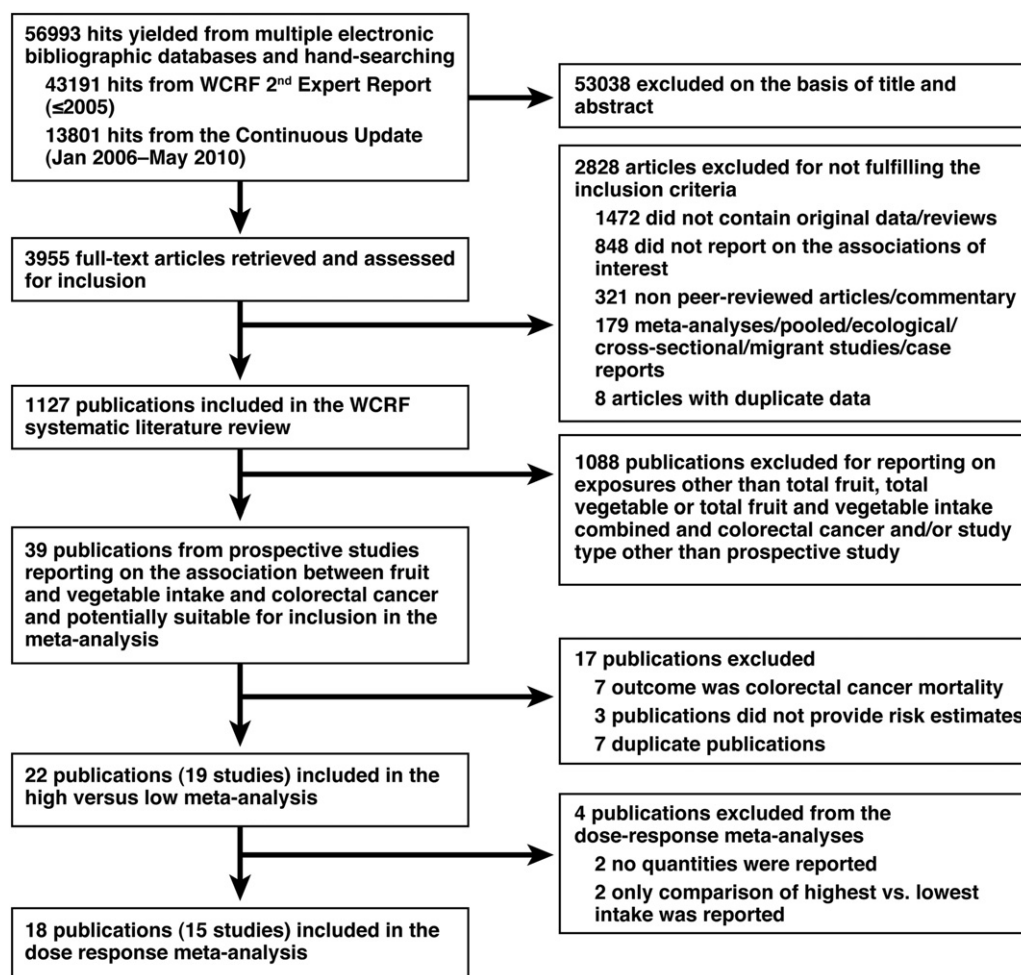


Figure 1. Flow chart of study selection.

search from June 2006 and up to May 2010 was conducted by 2 of the authors (DSMC and RL). Data were extracted into a database by 3 authors (DSMC, RL, and DA) and was checked for accuracy by 2 authors (DA and TN). We did not assess study quality using a quality score, but investigated whether specific study characteristics, such as duration of follow-up, number of cases, and adjustment for confounders, which are indicators of study quality, influenced the results in subgroup analyses.

Statistical Methods

To take into account heterogeneity between studies, we used a random effects models to calculate summary RRs and 95% CIs for the highest vs the lowest level of fruit and vegetable intake and for the dose-response analysis.³⁵ The average of the natural logarithm of the RRs was estimated and the RR from each study was weighted by the inverse of its variance. A 2-tailed $P < .05$ was considered statistically significant. For studies that reported results separately for men and women, but not combined, we combined the results using a fixed-effects model to obtain an overall estimate for both sexes. For studies that reported separately on colon and rectal cancer, but not for colorectal cancer, we used the method developed by Hamling et al to combine the results.³⁶ For 2 studies (1 publication)¹⁰ that did not provide the information required to apply the Hamling method, we used a fixed effects model to pool the results for colon and rectal cancer.

We used the method described by Greenland and Longnecker³⁷ for the dose-response analysis and computed study-specific slopes (linear trends) and 95% CIs from the natural logs of the RRs and CIs across categories of fruit and vegetable intake. The method requires that the distribution of cases and person-years or noncases and the RRs with the variance estimates for at least 3 quantitative exposure categories are known. We estimated the distribution of cases or person-years in studies that did not report these, but reported the total number of cases/person-years, if the results were analyzed by quantiles (and could be approximated). If this information was missing and the results were reported by functional categories, we used variance weighted least squares regression to estimate the slopes. We examined a potential nonlinear dose-response relationship between fruit and vegetable intakes and colorectal cancer using fractional polynomial models.³⁸ We determined the best-fitting second-order fractional polynomial regression model, defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity.³⁹ We present results using both linear and nonlinear models for comparison with previous meta-analyses that used linear models. The median or mean level of fruit and vegetable intake in each category of intake was assigned to the corresponding relative risk for each study when provided in the paper. For studies that reported fruit and vegetable intake by

ranges of intake, we estimated the mean intake in each category by calculating the average of the lower and upper bound. When the highest category was open-ended, we assumed the open-ended interval length to be the same as the adjacent interval. When the lowest category was open-ended, we set the lower boundary to 0. If the intakes were reported in densities (ie, g/1000 kcal or g/1000 kJ),^{11,28,29,31} we recalculated the reported intakes to absolute intakes using the mean or median energy intake. In studies that reported intakes as frequency, we used 80 g as a serving size for recalculation of the intakes to a common scale (g/d).²³ For one study that reported results in cup equivalents,³¹ we used 160 g as a cup equivalent size for vegetables because the definition of the cup equivalent for vegetables was twice as large as the definition of a serving per day from another paper from the same study (1 cup equivalent = 2 cups leafy vegetables or 1 cup other vegetables, 1 serving = 1 cup leafy vegetables, or ½ cup other vegetables).²⁸ The dose-response results are presented for a 100 g/d increment. Heterogeneity between studies was assessed using Q and I^2 statistics.⁴⁰

Potential sources of heterogeneity were investigated in subgroup and meta-regression analyses by sex, cancer subsite, duration of follow-up, number of cases, geographic location, and adjustment for confounding factors. Small-study bias, such as publication bias, was assessed using a funnel plot and Egger's test⁴¹ with results considered to indicate potential small-study bias when $P < .10$. In addition, we conducted sensitivity analyses excluding from the high vs low analysis the studies that were excluded from the dose-response analyses (because of insufficient data), and compared the summary RRs with those from all studies combined.

Stata version 10.1 software (StataCorp, College Station, TX) was used for the statistical analyses.

Results

We identified 19 cohort studies (22 publications)^{5,7-11,13,17-22,28-33,42-44} that were included in the analysis of the highest vs the lowest fruit and/or vegetable intake and colorectal cancer risk. Fifteen of these studies (18 publications)^{7-11,13,17-19,21,22,28,29,31-33,42-43} were included in the dose-response analysis (Table 1, Figure 1). Five of the studies were from Europe, 10 from America, and 4 from Asia.

Total Fruit and Vegetables

High vs low analysis. Eleven cohort studies (10 publications)^{9,10,18,19,21,22,28,29,32,33} investigated the association between total fruit and vegetable intakes and colorectal cancer risk and included 11,853 cases among 1,523,860 participants. For colorectal cancer, the summary RR for all studies was 0.92 (95% CI: 0.86-0.99), with little evidence of heterogeneity, $I^2 = 22\%$ and $P_{\text{heterogeneity}} = .24$ (Figure 2A). The inverse association was limited to colon cancer (Table 2).

Dose-response analysis. Eleven cohort studies (10 publications)^{9,10,18,19,21,22,28,29,32,33} were included in the

dose–response analysis of total fruit and vegetable intakes and colorectal cancer risk. The summary RR per 100 g/d was 0.99 (95% CI: 0.98–1.00), with little evidence of heterogeneity, $I^2 = 38\%$ and $P_{\text{heterogeneity}} = .10$ (Supplementary Figure 1A). Results were similar for colon and rectal cancer (Supplementary Figure 1A). Because of differences in the intake in the reference category among the studies, we could not fit an interpretable nonlinear model.

Fruits

High vs low analysis. Fourteen cohort studies^{5,8,9,11,17–22,29–32} were included in the analysis of high vs low fruit intake and colorectal cancer risk, including 14,876 cases among 1,558,147 participants. The summary RR was 0.90 (95% CI: 0.83–0.98), with moderate heterogeneity, $I^2 = 42\%$, $P_{\text{heterogeneity}} = .05$ (Figure 2B). The inverse association was again limited to colon cancer (Table 2, Figure 2B).

Dose–response analysis. Thirteen cohort studies (12 publications)^{8–11,17–19,21,22,29,31,32} were included in the dose–response analysis. The summary RR per 100 g/d was 0.98 (95% CI: 0.94–1.01), with moderate heterogeneity, $I^2 = 64\%$, $P_{\text{heterogeneity}} = .001$ (Supplementary Figure 1B). Similar results were observed for colon and rectal cancer (Supplementary Figure 1B). In meta-regression analyses, none of the study characteristics investigated were found to be significant predictors of the heterogeneity (geographic location, number of cases, sample size, duration of follow-up, adjustment for confounders), although there was a suggestion of a weaker effect in studies with adjustment for physical activity and body mass index ($P = .07$ for both, results not shown) compared with studies that did adjust for these covariates. There was evidence of a nonlinear association between fruit intake and colorectal cancer risk, $P_{\text{for nonlinearity}} < .001$, with most of the risk reduction observed when increasing intake up to about 100 g/d. Higher intakes were associated with a further, but more modest decrease in risk (Figure 3A).

Vegetables

High vs low analysis. Sixteen cohort studies (15 publications)^{5,8–11,17–22,29–32} were included in the analysis of high vs low vegetable intake and colorectal cancer, including 16,057 cases among 1,694,236 participants. The summary RR was 0.91 (95% CI: 0.86–0.96). There was no indication of heterogeneity, $I^2 = 0\%$, $P_{\text{heterogeneity}} = .54$ (Figure 2C). The inverse association was limited to colon cancer (Table 2, Figure 2C).

Dose–response analysis. Twelve cohort studies^{8–11,18,19,21,22,29,31,32} were included in the dose–response analysis. The summary RR per 100 g/d was 0.98 (95% CI: 0.97–0.99), with no indication of heterogeneity, $I^2 = 0\%$, $P_{\text{heterogeneity}} = .69$ (Supplementary Figure 1C). The inverse association was restricted to colon cancer (Supplementary Figure 1C). There was evidence for a nonlinear association between vegetable intake and colorectal cancer risk, $P_{\text{for nonlinearity}} = .001$, with the greatest reduction for an intake

between 100 and 200 g/d, but little evidence of a further reduction with higher intakes (Figure 3B).

Publication Bias, Subgroup, and Sensitivity Analyses

We found no indication of publication bias in the analyses, Egger's test showed $P = .52$ for fruit and vegetables and colorectal cancer, .79 for fruits, and .14 for vegetables. In stratified analyses (Table 2), the association between high vs low fruit and vegetable intake and colorectal cancer risk was inverse in all strata except in Asian studies, although in most analyses the associations were not statistically significant. There was no evidence that the results differed significantly by sex, $P \geq .26$ for all comparisons. In meta-regression analyses, only geographic location was found to modify the association between fruit and vegetables combined and colorectal cancer with a significant inverse association among European studies, but not among American or Asian studies, $P_{\text{heterogeneity}} = .03$ (Table 2). Asian studies did not provide evidence of an inverse association for either fruits or vegetables, although the tests for heterogeneity were not significant, $P_{\text{heterogeneity}} = .31$ and $P_{\text{heterogeneity}} = .43$, respectively.

In addition, to assess whether exclusion of studies from the dose–response analysis might have biased the results, we repeated the high vs low intake analyses restricted to the studies included in the dose–response analyses. The summary RRs for fruit and for vegetables and colorectal cancer risk were 0.89 (95% CI: 0.81–0.98) and 0.90 (95% CI: 0.85–0.95), respectively, almost identical to the results from the high vs low analyses including all studies.

We also assessed the influence of including studies on colorectal cancer mortality on our results. Five and one additional studies were included in the analysis of fruit^{6,12,14–16} and vegetables,⁶ respectively. The summary RR was 0.92 (95% CI: 0.85–1.00) for fruit with moderate heterogeneity, $I^2 = 40\%$, $P_{\text{heterogeneity}} = .04$ and .91 (95% CI: 0.87–0.96) for vegetables with no heterogeneity, $I^2 = 0\%$, $P_{\text{heterogeneity}} = .49$, similar to the original analysis.

Discussion

In this meta-analysis, high vs low intake of fruit, vegetables and fruit and vegetables combined were associated with small but statistically significant reductions in colorectal cancer risk. In the linear dose–response analysis, a significant inverse association was observed only for vegetables. However, we found for the first time in a meta-analysis, to our knowledge, evidence of a nonlinear inverse association between fruits and for vegetables and colorectal cancer risk, with the greatest reduction in risk at the lower range of intake.

The hypothesis that fruit and vegetable intake protects against colorectal cancer has received much interest both among medical professionals and the general population. In vitro, experimental animal studies and human feeding

Table 1. Prospective Studies of Fruits, Vegetable Intake, and Colorectal Cancer Risk

First author, y, country/region	Study name	Follow-up period	Study size, sex, age, number of cases	Dietary assessment	Exposure	Quantity	RR (95% CI)	Adjustment for confounders
Shibata, 1992, USA ⁴²	Leisure World Cohort Study	1981–1985 to 1989, 70,159 person-y follow-up	11,580 m and w, age 65–82 y: 97/105 CC cases (m/w)	FFQ, 59 food items	Fruit, vegetables, m	9.66 vs 4.14 serv/d	1.50 (0.91–2.46)	Age, smoking
					Vegetables	5.70 vs 2.16 serv/d	1.39 (0.84–2.30)	
					Fruit	4.38 vs 1.45 serv/d	1.12 (0.69–1.81)	
					Fruit, vegetables, w	10.06 vs 4.54 serv/d	0.63 (0.40–1.00)	
Steinmetz, 1994, USA ⁴³	Iowa Women's Health Study	1986–1990, 5 y follow-up, 167,447 person-years	35,216 w, age 55–69 y: 212 CC cases	Validated FFQ, 127 food items	Fruit, vegetables	≥47.1 vs <24.6 serv/wk	0.89 (0.57–1.40)	Age, smoking status, alcohol intake, total energy
					Vegetables	≥30.5 vs <15.1 serv/wk	0.73 (0.47–1.13)	
Kato, 1997, USA ⁵	New York University Women's Cohort Study	1985–1991 to 1994, 7.1 y follow-up, 105,044 person-years	14,727 w, age 34–65 y: 100 CRC cases	FFQ, 70 food items	Fruits	Quartile 4 vs 1	1.49 (0.82–2.70)	Age, total calories, place at enrollment, highest level of education
					Vegetables	Quartile 4 vs 1	1.63 (0.92–2.89)	
Zheng, 1998, USA ⁷	Iowa Women's Health Study	1986–1994, 9 y follow-up, 293,090 person-years	34,702 w, age 55–69 y: 144 RC cases	Validated FFQ, 127 food items	Fruit, vegetables	≥48.6 vs <33.5 serv/wk	0.97 (0.62–1.51)	Age
Pietinen, 1999, Finland ⁸	ATBC Cancer Prevention Study	1987–1995, 8 y follow-up	27,111 m (smokers), age 55–69 y: 185 CRC cases	Validated FFQ, 276 food items	Vegetables	191 vs 44 g/d	1.2 (0.8–1.9)	Age, supplement group, tobacco years, BMI, alcohol, education, physical activity at work, calcium, energy
					Fruit	216 vs 30 g/d	1.1 (0.8–1.7)	
Voorrips, 2000, Netherlands ⁹	Netherlands Cohort Study	1986–1992, 6.3 y follow-up, 17,478 person-years	58,279 m and 62,753 w, age 55–69 y. Total fruit & vegetables, vegetables: subcohort 1497/1456 m/w: 465/427 CRC cases 266/312 CC cases 199/115 RC cases Total fruits: Subcohort 1525/1497 m/w: 549/415 CRC cases 332/288 CC cases 217/127 RC cases	Validated FFQ, 150 food items	Fruit, vegetables, CC, m	519 vs 177 g/d	0.95 (0.64–1.41)	Age, FH – CRC, alcohol intake
					Vegetables	285 vs 100 g/d	0.85 (0.57–1.27)	
					Fruits	286 vs 34 g/d	1.33 (0.90–1.97)	
					Fruit, vegetables, CC, w	578 vs 208 g/d	0.66 (0.44–1.01)	
					Vegetables	293 vs 107 g/d	0.83 (0.54–1.26)	
					Fruits	343 vs 65 g/d	0.73 (0.48–1.11)	
					Fruit, vegetables, RC, m	519 vs 177 g/d	0.88 (0.56–1.37)	
					Vegetables	285 vs 100 g/d	0.88 (0.55–1.41)	
					Fruits	286 vs 34 g/d	0.85 (0.55–1.32)	
					Fruit, vegetables, RC, w	578 vs 208 g/d	1.17 (0.63–2.17)	
					Vegetables	293 vs 107 g/d	1.78 (0.94–3.38)	
					Fruits	343 vs 65 g/d	0.67 (0.34–1.33)	
Michels, 2000, USA ¹⁰	Health Professionals Follow-up Study & Nurses' Health Study	NHS: 1980–1996, 1,327,029 person-years HPFS: 1986–1996, 416,616 person-years Total: 1,743,645 person-years	88,764 w, age 34–59 y: 569 CC cases 155 RC cases 47325 m, age 40–75 y: 368 CC cases 244 RC cases Total: 937 CC cases 244 RC cases	Validated FFQ, 61–87 food items	Fruit, vegetables, all, CC	≥6 vs ≤2 serv/d	1.08 (0.84–1.38)	W (NHS): Age, FH – CRC, sigmoidoscopy, height, BMI, pack-years of smoking, alcohol, physical activity, menopausal status, postmenopausal HRT use, aspirin, vitamin supplement use, total calories, red meat M (HPFS): Age, FH – CRC, sigmoidoscopy, height, BMI, pack-years of smoking, alcohol, physical activity, aspirin, vitamin supplement use, total calories, red meat
					Fruit, vegetables, HPFS	≥6 vs ≤2 serv/d	1.28	
					Fruit, vegetables, NHS	≥6 vs ≤2 serv/d	0.96	
					Fruit, all	≥5 vs ≤1 serv/d	NC	
					Fruit, HPFS	≥5 vs ≤1 serv/d	1.35	
					Fruit, NHS	≥5 vs ≤1 serv/d	0.80	
					Vegetables, all	≥5 vs ≤1 serv/d	1.00 (0.72–1.38)	
					Vegetables, HPFS	≥5 vs ≤1 serv/d	1.24	
					Vegetables, NHS	≥5 vs ≤1 serv/d	0.96	
					Fruit, vegetables, all, RC	≥6 vs ≤2 serv/d	0.99 (0.62–1.56)	
					Fruit, vegetables, HPFS	≥6 vs ≤2 serv/d	1.20	
					Fruit, vegetables, NHS	≥6 vs ≤2 serv/d	0.88	
					Fruit, all	≥5 vs ≤1 serv/d	NC	
					Fruit, HPFS	≥5 vs ≤1 serv/d	2.04	
					Fruit, NHS	≥5 vs ≤1 serv/d	0.66	
					Vegetables, all	≥5 vs ≤1 serv/d	1.17 (0.63–2.18)	
					Vegetables, HPFS	≥5 vs ≤1 serv/d	0.67	
					Vegetables, NHS	≥5 vs ≤1 serv/d	1.24	

Table 1. Continued

First author, y, country/region	Study name	Follow-up period	Study size, sex, age, number of cases	Dietary assessment	Exposure	Quantity	RR (95% CI)	Adjustment for confounders
Terry, 2001, Sweden ²¹	Swedish Mammography Screening Cohort Study	1987–1990/1998, 9.6 y follow-up, 588,270 person-years	61463 w, age 40–74 y: 460 CRC 291 CC cases 159 RC cases 10 combined	Validated FFQ, 67 items	Fruit, vegetables, CRC	>5.0 vs <2.5 serv/d	0.73 (0.56–0.96)	Age, red meat, dairy products, total calories
					Vegetables	>2.0 vs <1.0 serv/d	0.84 (0.65–1.09)	
					Fruits	>2.0 vs <1.0 serv/d	0.68 (0.52–0.89)	
					Fruit, vegetables, CC	>5.0 vs <2.5 serv/d	0.81 (0.59–1.13)	
					Vegetables	>2.0 vs <1.0 serv/d	0.90 (0.66–1.24)	
					Fruits	>2.0 vs <1.0 serv/d	0.76 (0.55–1.06)	
					Fruit, vegetables, RC	>5.0 vs <2.5 serv/d	0.60 (0.38–0.96)	
					Vegetables	>2.0 vs <1.0 serv/d	0.71 (0.45–1.12)	
					Fruits	>2.0 vs <1.0 serv/d	0.54 (0.33–0.89)	
					Fruit, vegetables, RC	>5.0 vs <2.5 serv/d	1.15 (0.86–1.53)	
Fruit, vegetables, CC	>2.0 vs <1.0 serv/d	0.95 (0.71–1.26)						
Flood, 2002, USA ¹¹	Breast Cancer Detection & Demonstration Project	1987–1989 to 1998, 8.7 y follow-up, 386,142 person-years	45490 w, median age 61.8 y: 485 CRC cases	Validated FFQ, 62 items	Fruit, vegetables, CC	0.50 vs 0.05 serv/1000 kJ/d	1.15 (0.86–1.53)	Age, multivitamin use, BMI, height, NSAIDs, smoking status, education level, physical activity, grains, red meat, calcium, vitamin D, alcohol, nutrient density (total calories), mutual adjustment between fruits and vegetables
					Vegetables	0.98 vs 0.25 serv/1000 kJ/d	0.95 (0.71–1.26)	
McCullough, 2003, USA ¹³	Cancer Prevention Study 2 Nutrition Cohort	1992–1993 to 1997, 4.5 y follow-up	62,609 m and 70,554 w, age 50–74 y: 298/210 CC cases (m/w)	Validated FFQ, 68 food items	Fruit, m	≥6.2 vs 1.2 serv/d	1.11 (0.76–1.62)	Age, exercise METs, aspirin, smoking, FH – CRC, BMI, education, energy, multivitamin use, total calcium, red meat intake and HRT use (w)
					Vegetables	≥3.3 vs 1.3 serv/d	0.69 (0.47–1.03)	
					Fruit, vegetables	H vs I 5	1.23 (0.83–1.83)	
					Fruit, w	≥6.0 vs 1.2 serv/d	0.74 (0.47–1.16)	
					Vegetables	≥3.3 vs 1.3 serv/d	0.91 (0.56–1.48)	
Wu K, 2004, USA ⁴⁴	Health Professionals Follow-up Study	1986–2000, 14 y follow-up	47,311 men, age 40–75 y: 561 CC cases	Validated FFQ, 131 food items	Fruit, vegetables	H vs I 5	0.70 (0.43–1.15)	Age, FH – CRC, history of endoscopy, physical activity, pack-years of smoking before age 30, race, aspirin use, total energy, BMI
					Fruit	Quintile 5 vs 1	0.75 (0.56–1.00)	
					Fruit, vegetables	H vs I 5	0.70 (0.43–1.15)	
Sanjoaquin, 2004, England ¹⁷	Oxford Vegetarian Study	1980–1984 to 1999, 17 y follow-up	10,998 m and w, age 16–89 y: 95 CRC cases	FFQ (validated for fiber intake)	Fresh or dried fruit	≥10 vs <5/wk	0.60 (0.35–1.02)	Age, sex, alcohol, smoking
					Vegetables	Tertile 3 vs 1	0.86 (0.54–1.38)	
Lin, 2005, USA ¹⁸	Women’s Health Study	1993–2003, 10 years follow-up	36,976 w, age ≥45 years: 223 CRC cases	Validated FFQ, 131 food items	Fruit, vegetables	10.0 vs 2.6 serv/d	0.96 (0.58–1.62)	Age, randomized treatment assignment, BMI, FH – CRC in a 1 st -degree relative, history of colon polyps, physical activity, smoking status, baseline aspirin use, red meat intake, alcohol, total energy intake, menopausal status, HRT use
					Fruit	3.8 vs 0.6	0.79 (0.48–1.30)	
					Vegetables	6.8 vs 1.5	0.89 (0.56–1.41)	
Sato, 2005, Japan ¹⁹	Miyagi Cohort Study	1990–1997, 7 y follow up, 307,675 person-years	47,605 m and w, age 40–64 y: 165 CC cases 110 RC cases	Validated FFQ, 40 items	Fruit, vegetables, CC, all	≥698 vs ≤543 g/d	1.13 (0.73–1.75)	Age, sex, smoking status, alcohol, BMI, education, FH – cancer, walking time, meat consumption, energy
					Vegetables	≥313 vs ≤245 g/d	1.24 (0.79–1.95)	
					Fruit	≥242 vs ≤95 g/d	1.45 (0.85–2.47)	
					Fruit, vegetables, CC, m	≥698 vs ≤543 g/d	0.92 (0.54–1.59)	
					Vegetables	≥313 vs ≤245 g/d	1.00 (0.56–1.77)	
					Fruit	≥242 vs ≤95 g/d	1.75 (0.89–3.44)	
					Fruit, vegetables, CC, w	≥698 vs ≤543 g/d	1.55 (0.72–3.32)	
					Vegetables	≥313 vs ≤245 g/d	1.65 (0.78–3.49)	
					Fruit	≥242 vs ≤95 g/d	0.99 (0.23–4.25)	
					Fruit, vegetables, RC, all	≥698 vs ≤543 g/d	1.12 (0.67–1.89)	
					Vegetables	≥313 vs ≤245 g/d	1.14 (0.67–1.93)	
					Fruit	≥242 vs ≤95 g/d	1.41 (0.73–2.73)	
					Fruit, vegetables, RC, m	≥698 vs ≤543 g/d	1.10 (0.55–2.17)	
					Vegetables	≥313 vs ≤245 g/d	1.32 (0.67–2.60)	
					Fruit	≥242 vs ≤95 g/d	0.28 (0.04–2.09)	
					Fruit, vegetables, RC, w	≥698 vs ≤543 g/d	1.26 (0.56–2.86)	
Vegetables	≥313 vs ≤245 g/d	0.99 (0.42–2.32)						
Fruit	≥242 vs ≤95 g/d	1.53 (0.68–3.45)						

Table 1. Continued

First author, y, country/region	Study name	Follow-up period	Study size, sex, age, number of cases	Dietary assessment	Exposure	Quantity	RR (95% CI)	Adjustment for confounders
Tsubono, 2005, Japan ²⁰	Japan Public Health Center-based Cohort study 1 & 2	Cohort 1/2: 1990–1999/1993–1999, total 694,074 person-y follow-up	88,658 m and w, age 40–59 and age 40–69 y; 705 CRC cases	Cohort 1/2: validated FFQ 44/52 items	Fruit, CRC, all	Quartile 4 vs 1	0.92 (0.70–1.19)	Age, sex, Public Health Centre area, BMI, frequency of sports, smoking, alcohol, vitamin supplement use, quartiles of energy, cereals, meats and fish
					Vegetables	Quartile 4 vs 1	1.00 (0.79–1.27)	
					Fruit, CC	Quartile 4 vs 1	0.92 (0.66–1.28)	
					Vegetables	Quartile 4 vs 1	1.08 (0.80–1.45)	
					Fruit, RC	Quartile 4 vs 1	0.91 (0.59–1.40)	
					Vegetables	Quartile 4 vs 1	0.87 (0.58–1.31)	
					Fruit, CRC, m	Quartile 4 vs 1	1.06 (0.70–1.61)	
					Vegetables	Quartile 4 vs 1	1.18 (0.88–1.59)	
					Fruit, CC	Quartile 4 vs 1	1.02 (0.61–1.70)	
					Vegetables	Quartile 4 vs 1	1.24 (0.86–1.79)	
					Fruit, RC	Quartile 4 vs 1	1.19 (0.59–2.36)	
					Vegetables	Quartile 4 vs 1	1.06 (0.63–1.78)	
					Fruit, CRC, w	Quartile 4 vs 1	0.93 (0.61–1.42)	
					Vegetables	Quartile 4 vs 1	0.88 (0.57–1.35)	
					Fruit, CC	Quartile 4 vs 1	0.87 (0.49–1.52)	
					Vegetables	Quartile 4 vs 1	1.01 (0.58–1.76)	
McCarl, 2006, USA ²²	Iowa Women's Health Study	1986–2000, 15 y follow-up, 471,508 person-years	35197 w, age 55–69 y; 954 CRC cases	Validated FFQ, 127 food items	Fruit, vegetables	≥58.01 vs ≤27.4 serv/wk	0.90 (0.73–1.10)	Age
					Fruits	≥25.5 vs ≤9.8 serv/wk	0.79 (0.65–0.97)	
					Vegetables	≥34.5 vs ≤14.5 serv/wk	0.89 (0.73–1.08)	
					Fruit, vegetables, m, CRC	5.2 vs 1.4 serv/1000 kcal/d	0.91 (0.78–1.05)	
					Fruits, m, CC	2.9 vs 0.4 serv/1000 kcal/d	1.11 (0.93–1.32)	
					Fruits, m, RC	2.9 vs 0.4 serv/1000 kcal/d	0.99 (0.75–1.30)	
Park, 2007, USA ²⁸	NIH-AARP Diet and Health Study	1995–96 to 2000, 4.3 y follow-up, 2,121,664 person-years	488,043 m and w, age 50–71 y; 2972 CRC cases	Validated FFQ, 124 food items	Vegetables, m, CC	2.9 vs 0.4 serv/1000 kcal/d	0.84 (0.71–0.99)	Age, education, physical activity, smoking, alcohol consumption, red meat, dietary calcium, total energy
					Vegetables, m, RC	2.9 vs 0.4 serv/1000 kcal/d	0.81 (0.62–1.05)	
					Fruit, vegetables, w, CRC	2.8 vs 0.6 serv/1000 kcal/d	1.08 (0.86–1.35)	
					Fruits, w, CC	2.8 vs 0.6 serv/1000 kcal/d	0.96 (0.75–1.24)	
					Fruits, w, RC	2.8 vs 0.6 serv/1000 kcal/d	1.59 (1.04–2.44)	
					Vegetables, w, CC	2.8 vs 0.6 serv/1000 kcal/d	1.10 (0.86–1.40)	
					Vegetables, w, RC	2.8 vs 0.6 serv/1000 kcal/d	1.21 (0.80–1.83)	
					Fruit, vegetables, m	483.2 vs 134.7 g/1000 kcal/d	0.74 (0.59–0.93)	
					Vegetables	236.2 vs 71.9 g/1000 kcal/d	0.85 (0.69–1.05)	
					Fruit	236.2 vs 71.9 g/1000 kcal/d	0.80 (0.64–0.99)	
					Fruit, vegetables, w	295.9 vs 30.1 g/1000 kcal/d	1.04 (0.81–1.33)	
					Vegetables	295.9 vs 30.1 g/1000 kcal/d	0.94 (0.75–1.17)	
Nomura, 2008, USA ²⁹	Multiethnic Cohort Study	1993–96 to 2001, 7.3 y follow-up, >1.4 million person-years	85,903 m and 105,108 w, age 40–75 y; 1138/972 CRC cases (m/w) 734/617 CC cases 276/179 RC cases	Validated FFQ, 180 food items	Fruit	608.1 vs 176.3 g/1000 kcal/d	0.83 (0.65–1.06)	Age, ethnicity, time since cohort entry, FH – CRC, CR polyp, HRT (w), pack-years of cigarette smoking, BMI, vigorous activity, aspirin use, multivitamins, energy intake, alcohol, red meat, folate, vitamin D, calcium
					Vegetables	286.5 vs 85.5 g/1000 kcal/d		
					Fruit, vegetables, w	381.5 vs 47.3 g/1000 kcal/d		
					Vegetables			
					Fruit			
					Vegetables			

Table 1. Continued

First author, y, country/region	Study name	Follow-up period	Study size, sex, age, number of cases	Dietary assessment	Exposure	Quantity	RR (95% CI)	Adjustment for confounders
Butler, 2008, Singapore ³⁰	Singapore Chinese Health Study	1993–98 to 2005, 9.8 y follow-up	61,321 m and w, age 45–74 y; 961 CRC cases	Validated FFQ, 165 food items	Vegetables Fruits	Quartile 4 vs 1 Quartile 4 vs 1	0.98 (0.79–1.21) 0.89 (0.72–1.09)	Age, sex, dialect group, interview year, diabetes at baseline, smoking history, BMI, alcohol, education, physical activity, 1 st degree relative with CRC, total daily energy intake
George, 2009, USA ³¹	NIH-AARP Diet and Health Study	1995–96 to 2003, 8 years, 3,320,418 person-years	288109 m, age 50–71 y: 3421 CRC cases 195,229 w, age 50–71 y: 1618 CRC cases	Validated FFQ, 124 food items	Fruit, w Vegetables Fruit, m Vegetables	1.90–5.58 vs 0–0.60 cup equivalents/1000 kcal/d 1.43–4.38 vs 0–0.56 cup equivalents/1000 kcal/d 1.59–5.13 vs 0–0.44 cup equivalents/1000 kcal/d 1.10–3.25 vs 0.06–0.44 cup equivalents/1000 kcal/d	0.93 (0.79–1.09) 0.87 (0.74–1.02) 0.94 (0.84–1.05) 0.84 (0.75–0.93)	Age, smoking, energy intake, BMI, alcohol, physical activity, education, race, marital status, FH – cancer, menopausal HT, mutual adjustment between fruit and vegetables
van Duijnhoven, 2009, Europe ³²	European Prospective Investigation into Cancer and Nutrition	1992–2000 to 2006, 8.8 y follow-up, 3,978,204 person-years	452,755 m and w, age 35–70 y; 2819 CRC cases 1828 CC cases 255 overlapping, unspecified CC cases 991 RC cases	Validated FFQ, diet history and/or 14-day record	Fruit, vegetables, CRC Fruit, vegetables, CC Fruit, vegetables, RC Vegetables, CRC Vegetables, CC Vegetables, RC Fruits, CRC Fruits, CC Fruits, RC	>603.6 vs <221.1 g/d >603.6 vs <221.1 g/d >603.6 vs <221.1 g/d >284.47 vs <95.1 g/d >284.47 vs <95.1 g/d >284.47 vs <95.1 g/d >342.7 vs <92.8 g/d >342.7 vs <92.8 g/d >342.7 vs <92.8 g/d	0.86 (0.75–1.00) 0.76 (0.63–0.91) 1.09 (0.85–1.40) 0.92 (0.79–1.06) 0.85 (0.71–1.02) 1.04 (0.81–1.33) 0.88 (0.76–1.01) 0.84 (0.71–1.00) 0.96 (0.76–1.21)	Age, sex, center, energy from fat, energy from nonfat, weight, height, physical activity, smoking status, alcohol consumption, red and processed meat consumption, fish consumption, dietary fiber from cereal sources
Lee, 2009, China ³³	Shanghai Women's Health Study	1997–2000 to 2007, 7.4 y follow-up, 540,156 person-years	73,224 w, age 40–70 y: 394 CRC cases 236 CC cases 158 RC cases	Validated FFQ, 77 food items	Fruit, vegetables, CRC Fruit, vegetables, CC Fruit, vegetables, RC	≥663 vs <325 g/d ≥663 vs <325 g/d ≥663 vs <325 g/d	1.2 (0.9–1.6) 1.3 (0.8–1.9) 1.0 (0.6–1.7)	Age

BMI, body mass index; CC, colon cancer, CR, colorectal; CRC, colorectal cancer; FFQ, food frequency questionnaire; FH, family history; HPFS, Health Professionals Follow-up Study; HRT/HT, hormone therapy; m, men; MET, metabolic equivalent task; NC, not calculated; NHS, Nurses' Health Study; NIH-AARP, National Institutes of Health-American Association of Retired Persons; RC, rectal cancer; w, women; serv, serving.

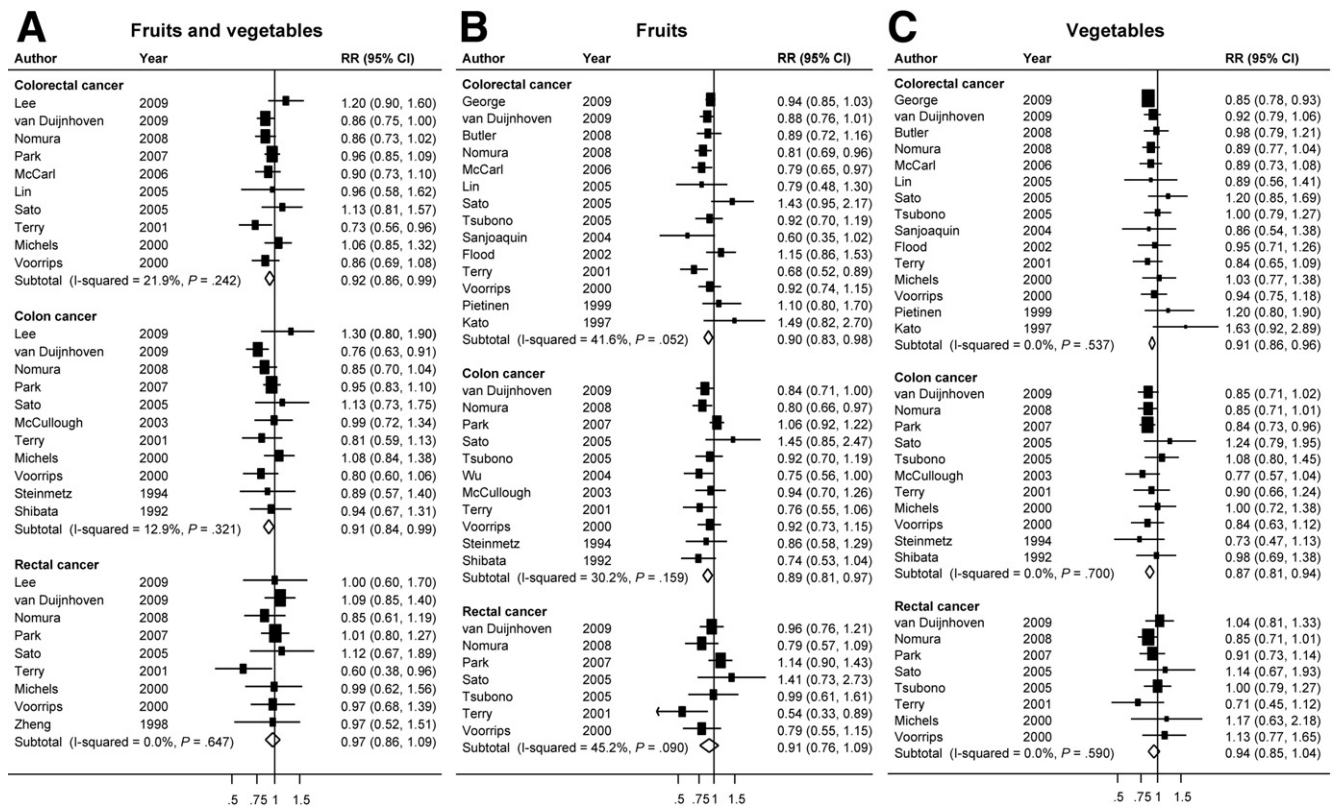


Figure 2. Fruits and vegetables and colorectal cancer, high vs low analysis.

studies have provided biologic plausibility for the hypothesis,^{2,3} but epidemiological studies have been inconsistent. Although the first report from the WCRF/AICR concluded that there was convincing evidence that intake of vegetables, but not fruit, protects against colorectal cancer, most of that evidence was based on case-control studies,⁴ which are liable to recall and selection biases. These results were generally not supported by subsequent cohort studies,^{5,8-10,13,18-20} several reviews and meta-analyses.²³⁻²⁶ In the second report from the WCRF/AICR, it was stated that there was limited suggestive evidence that fruit and nonstarchy vegetables protect against colorectal cancer, thus a downgrading of the judgment of the evidence since the first report.²⁷ Our linear dose-response analyses are consistent with the results from the second WCRF/AICR report, with the exception of vegetables, for which some recent large cohort studies^{33,34,36,37} may have contributed to the statistically significant inverse association we found. However, in contrast to previous meta-analyses, which have assumed a linear association between fruit and vegetables and colorectal cancer risk,^{23,27} we found evidence of a nonlinear inverse association, with the greatest risk reduction when increasing intake from low levels. The lack of significance of the results in the previous meta-analyses and for fruit in the present linear dose-response analysis might be because the linear model does not fit well with the data. Examining the shape of the dose-response curve seems to be important to clarify this association. This is compatible with the finding of a

significant inverse association in the high vs low meta-analysis.

The possible limitations of our meta-analysis must be taken into consideration. It is possible that the observed inverse association between fruit and vegetable intake and colorectal cancer risk could be due to unmeasured or residual confounding. Higher intake of fruit and vegetables is often associated with other lifestyle factors, including higher levels of physical activity, lower prevalence of smoking and overweight/obesity and lower intakes of alcohol and red and processed meat.^{31,32} However, most of the studies included in this meta-analysis adjusted for these and other potential confounders. Furthermore, in subgroup and meta-regression analyses, we found no significant heterogeneity between studies when stratified by whether they adjusted for confounding factors or not. Nevertheless, because we found weak associations and because individuals with very low intake of fruit and vegetables may have very different lifestyles compared with the general population we cannot exclude the possibility of residual confounding.

We did not find a consistent pattern of difference or heterogeneity in the results by sex, or any other study characteristics examined, except for geographic location, which significantly modified the association between fruit and vegetables combined and colorectal cancer risk. The strongest inverse association was found among European studies, but there was no evidence of a protective effect of fruits and vegetables in Asian studies. It is not clear

Table 2. Subgroup Analyses of Fruit and Vegetable Intakes and Colorectal Cancer, High vs Low Intake

	Total fruit and vegetables					Fruits					Vegetables				
	n	RR (95% CI)	I ² (%)	P _h ^a	P _h ^b	n	RR (95% CI)	I ² (%)	P _h ^a	P _h ^b	n	RR (95% CI)	I ² (%)	P _h ^a	P _h ^b
All studies	11	0.92 (0.86–0.99)	21.9	.24		14	0.90 (0.83–0.98)	41.6	.05		15	0.91 (0.86–0.96)	0	.53	
Duration of follow-up															
<10 y	7	0.91 (0.83–1.00)	38.5	.14	.52	11	0.93 (0.85–1.01)	43.9	.06	.16	11	0.92 (0.86–0.99)	17.1	.28	.97
≥10 y	4	0.97 (0.84–1.12)	0	.57		3	0.77 (0.64–0.91)	0	.64		4	0.92 (0.80–1.06)	0	.85	
Sex															
Men	5	0.87 (0.79–0.97)	0	.63	.042	7	0.94 (0.87–1.02)	1.0	.42	.26	7	0.91 (0.83–1.01)	21.9	.26	.75
Women	9	0.94 (0.83–1.06)	38.1	.11		11	0.87 (0.79–0.97)	32.3	.14		11	0.91 (0.84–0.98)	0	.64	
Men ^c	5	0.88 (0.80–0.97)	0	.58	.039	6	0.88 (0.80–0.98)	0	.60	.42	6	0.89 (0.82–0.98)	0	.59	.71
Women ^d	5	0.96 (0.82–1.13)	43.2	.13		6	0.93 (0.85–1.02)	6.8	.37		6	0.90 (0.83–0.99)	0	.64	
Subsite															
Colon	12	0.91 (0.84–0.99)	12.9	.32	.41	11	0.89 (0.81–0.98)	32.9	.14	.72	11	0.87 (0.81–0.94)	0	.70	.26
Rectum	10	0.97 (0.86–1.09)	0	.65		7	0.91 (0.76–1.09)	45.2	.09		8	0.94 (0.85–1.04)	0	.59	
Colon ^e	7	0.89 (0.79–0.99)	33.9	.17	.35	7	0.92 (0.82–1.04)	47.6	.08	.99	8	0.88 (0.81–0.95)	0	.60	.33
Rectum ^f	7	0.97 (0.85–1.10)	0	.42		7	0.91 (0.76–1.09)	45.2	.09		8	0.94 (0.85–1.04)	0	.59	
Proximal colon	5	0.89 (0.77–1.02)	0	.80	.43	5	0.96 (0.84–1.09)	0	.89	.99	6	0.89 (0.78–1.01)	0	.65	.97
Distal colon	5	0.80 (0.68–0.94)	10	.35		5	0.96 (0.85–1.09)	0	.62		6	0.89 (0.79–1.01)	0	.58	
Geographic location															
Europe	3	0.84 (0.75–0.93)	0	.55	.03	5	0.85 (0.73–0.99)	40.9	.15	.31	5	0.92 (0.83–1.02)	0	.73	.43
America	6	0.94 (0.86–1.02)	0	.64		6	0.91 (0.80–1.03)	48.6	.08		7	0.89 (0.83–0.96)	7.2	.37	
Asia	2	1.17 (0.94–1.45)	0	.79		3	1.00 (0.79–1.28)	50.6	.13		3	1.02 (0.89–1.18)	0	.60	
Number of cases															
<500	5	0.95 (0.78–1.15)	49.6	.09	.63	8	0.96 (0.78–1.18)	60.2	.01	.55	8	0.98 (0.87–1.10)	3.0	.41	.09
500 to <1500	3	0.97 (0.83–1.14)	12.0	.29		3	0.85 (0.75–0.97)	0	.61		4	0.96 (0.86–1.08)	0	.81	
≥1500	3	0.90 (0.83–0.98)	0	.43		3	0.89 (0.82–0.97)	18.2	.29		3	0.87 (0.82–0.93)	0	.64	
Adjustment for confounders															
Alcohol															
Yes	8	0.92 (0.86–0.99)	0	.50	.89	11	0.92 (0.85–0.99)	24.7	.21	.17	12	0.91 (0.86–0.96)	0	.67	.93
No	3	0.92 (0.71–1.19)	67.4	.05		3	0.83 (0.62–1.12)	63.9	.06		3	0.95 (0.74–1.23)	54.6	.11	
Smoking															
Yes	7	0.93 (0.86–1.00)	0	.42	.65	10	0.92 (0.84–1.01)	32.2	.15	.31	11	0.91 (0.86–0.96)	0	.59	.97
No	4	0.90 (0.75–1.07)	52.5	.10		4	0.85 (0.69–1.04)	56.4	.08		4	0.93 (0.79–1.09)	32.7	.22	
Body mass index, weight, WHR															
Yes	6	0.92 (0.83–1.02)	12.2	.34	.94	9	0.93 (0.85–1.01)	26.1	.21	.19	10	0.91 (0.86–0.96)	0	.50	.96
No	5	0.92 (0.81–1.04)	42.2	.14		5	0.82 (0.67–0.99)	51.2	.09		5	0.92 (0.80–1.05)	11.7	.34	
Physical activity															
Yes	7	0.93 (0.86–1.00)	0	.42	.65	9	0.93 (0.85–1.01)	26.1	.21	.19	10	0.91 (0.86–0.96)	0	.50	.96
No	4	0.90 (0.75–1.07)	52.5	.10		5	0.82 (0.67–0.99)	51.2	.09		5	0.92 (0.80–1.05)	11.7	.34	
Red, processed meat															
Yes	8	0.91 (0.84–1.00)	23.3	.25	.73	7	0.90 (0.78–1.04)	55.3	.04	.82	8	0.93 (0.86–1.01)	0	.79	.41
No	3	0.95 (0.80–1.14)	43.6	.17		7	0.91 (0.82–1.01)	27.8	.22		7	0.92 (0.83–1.02)	26.8	.22	
Dairy products, calcium intake															
Yes	3	0.88 (0.76–1.00)	44.9	.16	.36	4	0.89 (0.71–1.12)	66.6	.03	.66	4	0.91 (0.81–1.02)	0	.55	.85
No	8	0.95 (0.86–1.05)	18.4	.29		10	0.91 (0.83–0.99)	27.9	.19		11	0.92 (0.86–0.98)	7.1	.38	
Energy intake															
Yes	8	0.91 (0.84–1.00)	23.3	.25	.73	11	0.92 (0.84–1.02)	44.9	.05	.35	12	0.93 (0.87–0.99)	13.3	.31	.84
No	3	0.95 (0.80–1.14)	43.6	.17		3	0.82 (0.70–0.97)	19.4	.29		3	0.91 (0.79–1.04)	0	.91	

NOTE. n denotes the number of risk estimates, the number of studies used is higher in some analyses as 1 publication reported a combined estimate for 2 studies (reference number 13). WHR, waist-to-hip ration.
^aP value for heterogeneity within each subgroup.
^bP value for heterogeneity between subgroups with meta-regression analysis.
^{c,d}Subgroup analyses restricted to studies that reported results both for men and women.
^{e,f}Subgroup analyses restricted to studies that reported results for both colon and rectum.

whether this is a chance finding, because there were only 2 Asian studies in this subgroup analysis, or whether it could be due to genetic or other factors. It is also possible that differences in the ranges of intake or differences in the intake in the referent category could explain these results. Because of the nonlinear association between fruit and vegetables and colorectal cancer risk with the strongest reduction at low levels of intake, it is possible that some studies may have missed an effect because the intake in the referent category already may have been sufficient to reduce risk. For example, the mean intake of fruits and vegetables in the reference category was 155 g/d for the European studies, but it was 200 and 217 g/d for the American and Asian studies, respectively. For fruits and vegetables separately, the figures were 37 and 58 g/d for

European studies, 51 and 103 g/d for the American studies, and 48 g/d and 123 g/d for the Asian studies. Another possibility is that the studies differ by types of fruits and vegetables consumed. In addition, production methods, storage conditions, nutrient content, and cooking and preparation methods may also differ across studies. Further cohort studies of specific fruits and vegetables and colorectal cancer risk in different populations are needed.

Analyses of high vs low intakes are limited because true differences in the level and range of intake between studies are not taken into account and this may contribute to heterogeneity in the results. We also conducted linear and nonlinear dose–response analyses. The data required for dose–response analyses were not always present in the articles, thus some studies were excluded from these anal-

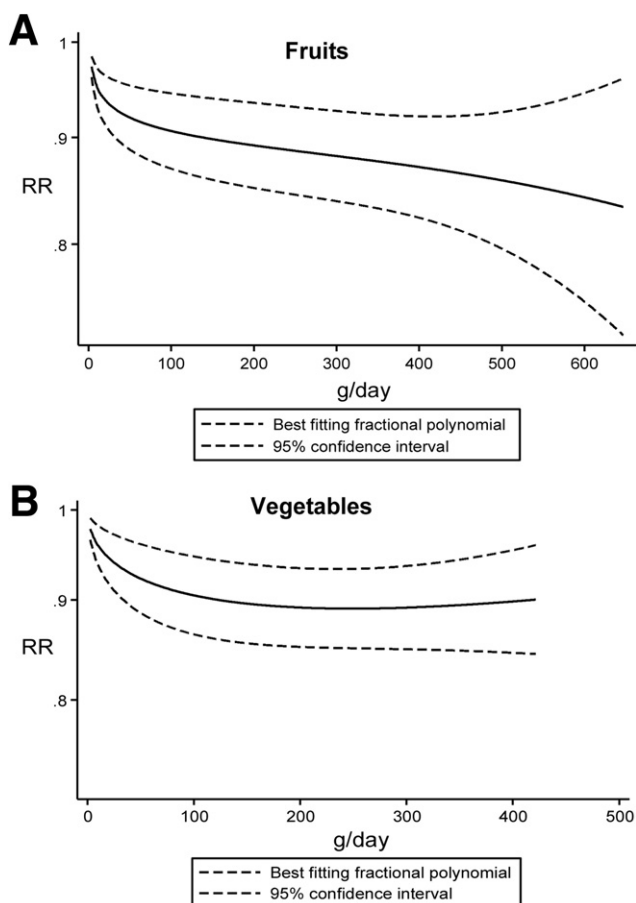


Figure 3. Fruits and vegetables and colorectal cancer, nonlinear dose-response analysis.

yses and this could potentially influence the dose-response results.⁴⁵ However, when we repeated the high vs low analyses with the same studies that were included in the dose-response analysis, results were similar to the original analyses. The results of the high vs low meta-analyses are consistent with those of the nonlinear dose-response analysis, whereas in general no association was observed when linear models were used.

Measurement errors in the assessment of dietary intake are known to bias effect estimates. We cannot exclude the possibility that measurement errors might have resulted in attenuated associations and that such attenuation might explain, in part, why the associations we observed are weak. Dietary changes after baseline can also attenuate associations between dietary intake and cancer risk, however, only 2 of the included studies used repeated assessments of diet and the results were similar when using only the baseline questionnaire for the analyses.¹⁰ Almost all the studies included in our meta-analysis used validated food frequency questionnaires, but only one of the studies corrected the risk estimates for measurement error.³² The estimates did not differ substantially before and after measurement error correction (RR = 0.98, 95% CI: 0.97–1.00 vs 0.97, 95% CI: 0.93–1.01 per 100 g/d fruit and vegetable intake, respectively). Any further studies might benefit from incorporating biomarkers of fruit and vege-

table intakes in the analyses.⁴⁶ Finally, because all the studies published to date have been conducted primarily among middle-aged and older persons, we cannot exclude the possibility that fruit and vegetable intakes in earlier periods of life might protect more strongly against colorectal cancer.

Although publication bias can be a problem in meta-analyses of published studies, we found no statistical evidence of publication bias in this meta-analysis and there was also no asymmetry in the funnel plots when inspected visually.

Several potential mechanisms might explain an inverse association between fruit and vegetables and colorectal cancer risk. Fruit and vegetables are good sources of fiber that can prevent colorectal cancer by increasing stool bulk, decreasing transit time in the colon, and diluting potential carcinogens.²⁷ We found an inverse association between fruit and vegetable intake and colon cancer, but little evidence of an inverse association with rectal cancer. Fewer studies conducted analyses of rectal cancer, and this might have limited our statistical power to detect an association. However, as observed for physical activity,²⁷ a real difference in the effects on colon and rectal cancer risk might also exist for fruit and vegetables. Both physical activity and high fiber intake can decrease the transit time in the colon without altering the storage time in the rectum and can account for the differences in the results for the 2 sites, but other mechanisms might also explain these observations. Fruit and vegetables are also good sources of folate, which has been associated with decreased risk of colorectal cancer in a number of studies,⁴⁷ but not all studies.²⁷ Folate plays an important role in DNA methylation and is necessary for synthesis of thymine. Folate deficiency can lead to misincorporation of uracil instead of thymine into DNA⁴⁸ and increase the number of chromosomal breaks.⁴⁹ In addition, fruit and vegetables are good sources of various antioxidants, vitamins, minerals, and other bioactive compounds, including flavonoids, carotenoids, glucosinolates, indoles, isothiocyanates, and selenium, which might prevent cancer by inducing the activity of detoxifying enzymes, reducing oxidative stress and inflammation.² High intake of fruit and vegetables can also decrease the risk of overweight/obesity,⁵⁰ which is an established risk factor for colorectal cancer.²⁷ The specific mechanism(s) that can explain the threshold effect we observed warrant further investigation.

Our meta-analysis also has several strengths. Because we based our analyses on prospective studies, we have minimized the possibility that our findings might be due to recall and selection bias. The studies included a larger number of cases and participants than any previous meta-analysis on the topic that we are aware of, with a total of approximately 1.5–1.7 million participants and 11,800–16,000 cases. Thus, we had statistical power to detect moderate and weak associations. It is likely that the weak inverse associations found in this meta-analysis are too weak to be detected in most individual cohort studies

and only possible to detect in meta-analyses or pooled analyses of numerous large cohort studies. Although the size of the association did not differ significantly in analyses stratified by study size, the overall associations were statistically significant only in the strata of studies with ≥ 1500 cases.

To our knowledge this is also the first meta-analysis to explore the potential nonlinear association of fruit and vegetable intake with colorectal cancer risk. Although some caution is needed in interpreting the exact quantities and size of the risk estimates because of the measurement errors associated with use of the dietary assessment methods, our results indicate that there is a low threshold level of between 100 and 200 g/d that can reduce risk about 10%. Above that level there seems to be no additional benefit of increasing vegetable intake in terms of colorectal cancer risk, and for fruit a slight further reduction with higher intakes is observed (an approximate 15% reduction for an intake of 600 g/d). Thus, from a public health perspective, targeting individuals and populations with a low fruit and vegetable intake might be most effective for colorectal cancer prevention. Nevertheless, public health recommendations for a high fruit and vegetable intake are justified because of the greater reductions in risk of coronary heart disease,⁵¹ stroke,⁵² and other cancers²⁷ associated with higher levels of fruit and vegetable intake.

In conclusion, our results suggest that there is a weak and nonlinear inverse association between intake of fruit and vegetables and colorectal cancer risk, with the greatest reduction in risk when increasing intake from very low levels. Further cohort studies are warranted to investigate specific types of fruit and vegetables, the impact of measurement errors on estimates, whether similar associations are found in non-white populations and using biomarkers of fruit and vegetable intake.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: [10.1053/j.gastro.2011.04.013](https://doi.org/10.1053/j.gastro.2011.04.013).

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Conflicts of interest

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