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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 ($P_{nonlinearity} < .001$) and vegetables ($P_{nonlinearity} = .001$). 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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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 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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Materials and Methods

Search Strategy

We updated the systematic literature review published in 2007[27] 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

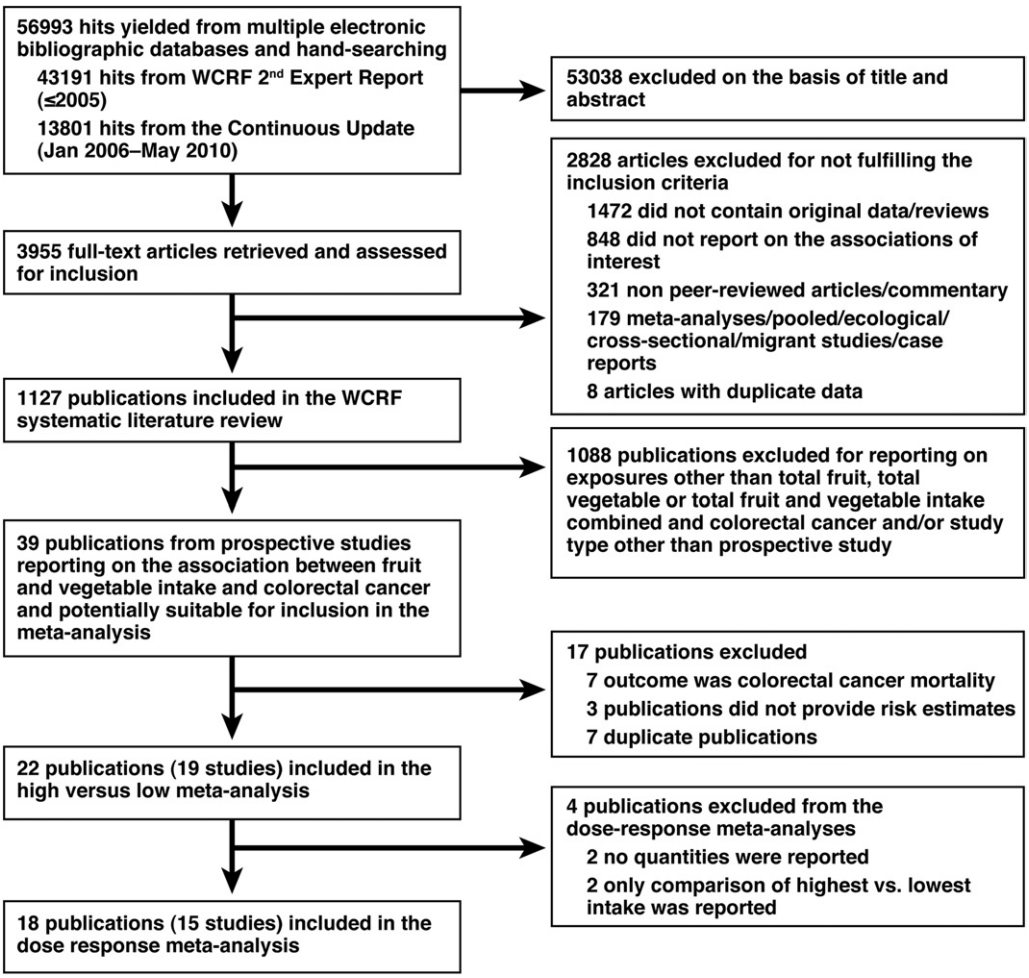

Figure 1. Flow chart of study selection.