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Consumption of fruit, but not vegetables, may reduce risk of gastric cancer: Results from a meta-analysis of cohort studies

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Abstract ***Background and aims:*** Quantification of the association between consumption of fruit and vegetables and risk of gastric cancer (GC) is controversial. We aimed to conduct a meta-analysis of cohort studies to evaluate the associations.
Methods: Eligible studies published up to 31st August 2013 were retrieved via both computer searches of PubMed and EMBASE and a manual review of references. Random-effects models were used to calculate summary relative risk (SRR). Heterogeneity among studies was assessed using Cochran's Q and I^2 statistics.
Results: A total of 17 articles (24 studies), were included in this meta-analysis. There were >2.4 million individuals (6632 GC events) with a median follow-up of 10 years. Based on the high versus low analysis, consumption of fruit, but not vegetables, may reduce risk of gastric cancer (fruit: SRR = 0.90, 95% confidence interval (CI): 0.83–0.98, $P_{\text{heterogeneity}} = 0.450$; vegetable: SRR = 0.96, 95% CI: 0.88–1.06, $P_{\text{heterogeneity}} = 0.150$). Meta regression analysis suggested that outcome (incidence versus mortality) and study quality (high versus low) contributed significantly to heterogeneity. The same results were also shown in the linear dose–response analysis (per 100-g/day) (fruit: SRR = 0.95, 95% CI: 0.91–0.99; vegetable: SRR = 0.96, 95% CI: 0.91–1.01). Significant inverse associations emerged in non-linear models for consumption of fruit ($P_{\text{non-linearity}} = 0.04$), but not for consumption of vegetables ($P_{\text{non-linearity}} = 0.551$).
Conclusions: Findings from this meta-analysis indicate a significant protective effect for the consumption of fruit on GC risk, but not for the consumption of vegetables.

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1. Introduction

Worldwide, gastric cancer (GC) remains the second leading cause of death due to cancer, although both the incidence and mortality rates of gastric cancer have been on the decline for the past century [1,2]. Infection with *Helicobacter pylori* has been recognised as the strongest risk factor for gastric cancer [3] and may even be a (close to) necessary condition for the development of gastric non-cardia adenocarcinoma (GNCA) [4]. Epidemiological studies have suggested that dietary factors play an important role in the aetiology of GC, but the specific dietary components involved remain unclear, except for the consumption of salt and salt-preserved foods [5,6], and alcohol abuse [7].

The consumption of vegetables and fruit has long been of interest for their possible favourable effect on risk of cancers. These foods contain many substances, such as vitamin C, vitamin E, folate, carotenoids and flavonoids, which are believed to prevent the formation of nitrosamines and neutralise the action of preformed nitrosamides, modulate DNA methylation, induce detoxifying phase II enzymes and promote apoptosis [8,9]. Based on a narrative review in 2007, the Working Group from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) reported that although a significant decreased risk for total vegetables and fruit was observed in case-control studies, a non-significant decreased risk was observed in cohort studies [10]. Case-control studies are more subject to recall and selection bias compared to cohort studies because of their retrospective nature, which can be of importance when investigating diet and gastrointestinal cancer. Thus, the Working Group concluded that high consumption of vegetables and fruit 'probably' protects against the development of gastric cancer [11].

Since this article's publication, a lot of prospective cohort analyses of fruit and vegetable consumption and gastric cancer risk have been published with mixed results [12–19]. Therefore, to better characterise this issue, we conducted a comprehensive meta-analysis of cohort studies by using our own methods and criteria. Furthermore, we evaluated the risk associations according to sex, gastric cancer subtypes (gastric cardia adenocarcinoma [GCA] and GNCA), study quality score, outcome, duration of follow-up and important confounding factors. We also examined the shape of the dose–response relationship (i.e. whether there are any threshold effects) by conducting non-linear dose–response analyses.

2. Methods

2.1. Literature search

This meta-analysis was planned, conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20]. Two investigators (C.Y. and W.Q.B.) sought to identify all epidemiologic studies by searching MEDLINE and EMBASE through August 2013 and by hand-searching the reference list of the computer retrieved articles. We searched for relevant studies with the following text words and/or Medical Subject Heading terms: (1) gastric OR stomach OR cardia; (2) cancer OR carcinoma OR neoplasia OR adenocarcinoma; (3) nutrition OR diet OR lifestyle OR fruit OR vegetable OR dietary OR consumption and (4) risk OR incidence OR prevalence OR mortality. Only articles written in English were included.

2.2. Definitions of exposure

As in the previous meta-analysis [21], we included the studies evaluating fruit or vegetable groups classified as 'all' or 'total' in this analysis. Studies that reported 'fresh vegetables' or 'fresh fruit' were also included under the consideration that it accounts for a very high proportion of the total consumption as previously reported [21]. Studies were excluded if they presented exposures as raw vegetables, cooked vegetables, green-yellow vegetables, other vegetables, citrus fruits, apple fruits or other fruit, because these items were not taken as equivalent to 'all' or 'total' [21].

2.3. Study selection

To be included, studies had to: (1) have original data from a cohort design; (2) report an association between total vegetables and/or total fruits and GC incidence or GC mortality; and (3) report the form of the relative risk (RR) with the 95% confidence intervals (CIs) at least adjusted or matched for age. Non-peer-reviewed articles, ecologic assessments, correlation studies, cross-sectional and retrospective studies and mechanistic studies were not included. If results based on the same study population were reported in more than one study, we included the one with the largest number of cases. We excluded studies on atomic-bomb survivors [22,23]. Two investigators (C.Y. and W.Q.B.) independently reviewed all potentially relevant articles to determine whether an article met the general inclusion criteria and disagreement was resolved by discussion between the investigators.

2.4. Data extraction

From each study, the following characteristics were extracted by two researchers (C.Y. and W.Q.B.): the name of the first author, publication year, geographic locations, the number and age of the subjects, the methods used for collection of data on exposure and determining the outcomes, duration of follow-up, confounding factors and the RR estimates with the