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Meta-analysis

Association between fruit and vegetable intake and risk for glioma: A meta-analysis

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ABSTRACT

Objective: Epidemiologic studies evaluating the association between the intake of vegetables and fruit and the risk for glioma have produced inconsistent results. Therefore, the aim of this study was to test the hypothesis that higher vegetable and fruit intake may have a protective effect on risk for glioma.

Methods: Pertinent studies were identified by a search in PubMed, Web of Knowledge, and Wan Fang Med Online up to January 2014. Random-effect model was used to combine study-specific results. Publication bias was estimated using Begg's funnel plot and Egger's regression asymmetry test.

Results: Fifteen studies involving 5562 cases focusing on vegetable intake and 17 studies involving 3994 cases of fruit intake compared with the risk for glioma were included in this meta-analysis. The combined relative risk (RR) of glioma associated with vegetable intake was 0.775 (95% confidence interval [CI], 0.688–0.872) overall, and the association for subgroup analysis by study design, sources of control, ethnicity, and number of cases was consistent with overall data. For fruit intake and glioma risk, significant protective associations were found in an Asian population (RR, 0.573; 95% CI, 0.346–0.947), but not in a white population. No publication bias was found.

Conclusions: This analysis indicated that intake of vegetables might have a protective effect on glioma. The intake of fruit might have a protective effect on glioma in the Asian population; however, the results need to be confirmed.

Introduction

Glioma is the most common primary brain tumor, occurring most frequently in adults and accounting for approximately 70% of adult brain malignancies [1,2]. It has an incidence of 5 to 10 cases per 100 000 [1]. Evidence has suggested that a genetic predisposition and ionizing radiation are established risk factors for brain tumors [3–5]. Additionally, other potential risk factors include exposure to environmental chemical carcinogens, such as chemical agents and, among dietary factors, exposure to N-nitroso compounds [1,3]. Due to the highly invasive character of glioma, complete resection is difficult to achieve [6]. Thus, prevention of glioma progression has become an important strategy for fighting the disease [7].

The intake of fruit and vegetables has long been associated with a decreased risk for various diseases [8,9]. The suggested mechanisms for the major role of vegetables and fruit include modulation of DNA methylation; protection from and repair of DNA damage; promotion of apoptosis; and induction of detoxifying phase II enzymes [10]. To date, a number of epidemiologic studies have explored the relationship between fruit and vegetable intake and the risk for glioma. However, results are not consistent [11–14]. Thus, to better characterize this issue, we conducted a comprehensive meta-analysis to evaluate the evidence from observational studies on the association between vegetable and fruit intake and the risk for glioma by summarizing it quantitatively with a meta-analysis approach.

Methods

Search strategy

A comprehensive search was conducted for available articles published in English or Chinese using the databases of PubMed, Web of Knowledge, and Wan Fang Med Online up to January 2014 and by hand-searching the reference lists of the computer-retrieved articles. The following search terms were used: *glioma* AND (neoplasm OR carcinoma OR cancer) combined with *nutrition OR diet OR lifestyle OR fruit OR vegetable*. Two investigators searched articles and reviewed all

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retrieved studies independently. Disagreements between the two investigators were resolved by consensus with a third reviewer.

Inclusion criteria

All relevant studies reporting the association of vegetable and fruit intake and glioma risk were considered for inclusion. The inclusion criteria were as follows: 1) used a case–control, nested case–control, or cohort design; 2) the exposure of interest were vegetables or fruit; 3) the outcome of interest was glioma; 4) associations reported in the form of relative risk (RR) (or odds ratio [OR]) with 95% confidence intervals (CI) for vegetables or fruit or providing sufficient information to calculate them. Accordingly, the following exclusion criteria were also used: reviews and repeated or overlapped publications. In the present meta-analysis, we included the studies evaluating fruit or vegetable groups classified as “all” or “total.” Exposures presented as cooked, raw, other vegetables; citrus or other fruits were not considered as equivalent to “all” or “total” and thus were not included. Studies that reported “fresh vegetables” or “fresh fruit” were included because fresh vegetables or fruit account for a very high proportion of total consumption.

Data extraction

Two researchers independently extracted the following information: name of the first author, publication year, study design, ethnicity, number of cases and controls or participants, type of controls, methods used for collection of data on exposure, exposure classification, confounders adjusted for, and the RR estimates with corresponding 95% CI for the highest versus lowest levels. From each study, we extracted the risk estimates adjusted for the greatest number of potential confounders. If there was disagreement between the two investigators about eligibility of the data, it was resolved by consensus with a third reviewer.

Statistical analysis

The pooled measure was calculated as the inverse variance-weighted mean of the natural logarithm of multivariate adjusted RR with 95% CI for the highest versus lowest levels to assess the association of vegetable and fruit intake with the risk for glioma. A random-effects model was used to combine study-specific RR (95% CI), which considers both within- and between-study variations [15]. The Q test and I^2 described previously [16] were used to assess heterogeneity among included studies. I^2 describes the proportion of total variation attributable to between-study heterogeneity as opposed to random error or chance, and I^2 values of 0, 25%, 50%, and 75% represent no, low, moderate, and high heterogeneity, respectively [17]. Meta-regression with restricted maximum likelihood estimation was performed to describe the potentially important covariates [18]. If no significant covariates were found to be heterogeneous, the subgroup analysis was conducted. Publication bias was estimated using Begg’s funnel plot [19] and Egger’s regression asymmetry test [20]. A study of influence analysis [21] was conducted to describe how robust the pooled estimator is to removal of individual studies. An individual study is suspected of excessive influence, if the point estimate of its omitted analysis lies outside the 95% CI of the combined analysis. All analyses were conducted using STATA software, version 11.0 (StataCorp LP, College Station, TX, USA). Two-tailed $P \leq 0.05$ was accepted as statistically significant.

Results

Search results and study characteristics

The search strategy identified 312 articles from PubMed, 11 from Wan Fang Med Online, and 432 from the Web of Knowledge. Twenty-nine articles were reviewed in full after reading the title/abstract. By studying reference lists, we identified two additional articles. Sixteen of these 31 articles were subsequently excluded from the meta-analysis for various reasons. Hence, 12 articles [12–14,22–30] with 15 studies (1 prospective study and 14 case–control studies) involving 5562 cases about vegetable intake and glioma risk and 15 articles [11–13,22–33] with 17 studies (2 prospective studies and 15 case–control studies) involving 3994 cases about fruit intake and glioma risk were used in this meta-analysis. The detailed steps of the literature search are shown in Figure 1. The characteristics of these studies are presented in Table 1.

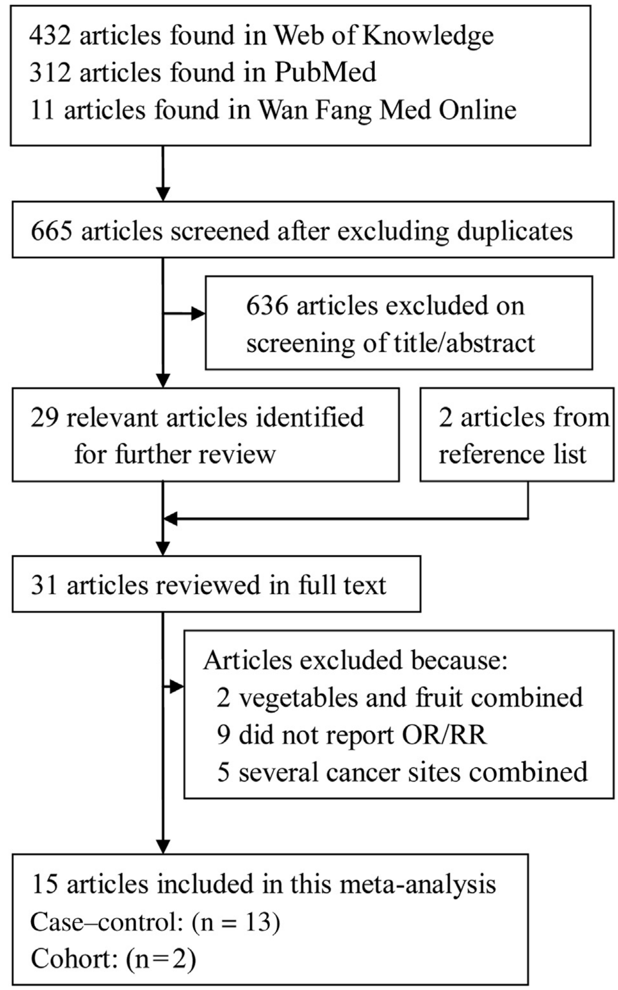

Fig. 1. Detailed steps of literature search. OR, odds ratio; RR, relative risk.

Total vegetables

High versus low analyses

For vegetable intake and glioma, data from 15 studies (1 prospective study and 14 case–control studies) including 5562 glioma cases were used. Inverse association of vegetable intake with risk for glioma was reported in seven studies, and no significant association of vegetable intake with risk for glioma was reported in eight studies. Pooled results suggested that highest versus lowest level vegetable intake was significantly associated with the risk for glioma (summary RR, 0.775; 95% CI, 0.688–0.872; $I^2 = 41.3\%$; $P_{heterogeneity} = 0.048$) (Fig. 2).

Sources of heterogeneity and subgroup analyses

As seen in Figure 2, moderate of heterogeneity ($I^2 = 41.3\%$; $P_{heterogeneity} = 0.048$) was found in the pooled results. However, univariate meta-regression analysis, with the covariates of publication year, ethnicity, number of cases, and sources of controls showed no covariate having a significant effect on between-study heterogeneity, respectively.

Fourteen case–control studies were included in this meta-analysis, and the pooled RR was 0.757 (95% CI, 0.675–0.850) for the highest versus the lowest category of vegetable intake and glioma risk. In subgroup analyses of ethnicity, when we restricted