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Original Article

Dietary nitrite and nitrate is not associated with adult glioma risk: a meta-analysis

Peng Wang[2*], Chong-Xian Hou[1,2*], Yan-Wen Li[2], Dong Zhou[2]

[1]*Southern Medical University, Guangdong, P. R. China;* [2]*Department of Neurosurgery, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, P. R. China.* [*]*Co-first authors.*

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Abstract: Background: Nitrite and nitrate are precursors of N-Nitroso compounds (NOCs) which have been confirmed as potent animal carcinogens and potential human carcinogens. Thus, we conducted this meta-analysis to examine the possible association of dietary nitrite and nitrate with the risk of glioma in adults. Methods: Pertinent studies were identified by a search in Pubmed and Embase up to August 2015. The random- or fixed-effects model was used to combine the results depending on the heterogeneity of the analysis. Results: Nine studies including 2264 adult glioma cases about dietary intake of nitrite and nitrate with the risk of glioma were included in this meta-analysis. The combined odd ratio (OR) of adult glioma associated with dietary nitrite and nitrate intake was 1.17 (95% CI = 0.99-1.35) and 0.89 (95% CI = 0.66-1.12) respectively. Conclusions: Our analysis suggested that dietary nitrate and nitrite are not associated with the risk of adult glioma.

Keywords: Diet, nitrite, nitrate, glioma, meta-analysis

Introduction

Glioma is the most common primary malignant brain tumor. In USA, it represents 31% of all central nervous system (CNS) tumors [1]. However, the treatment of glioma remains a difficulty because of the high rates of recurrence, morbidity and mortality. Therefore, the prevention of glioma is of particular importance.

N-Nitroso compounds (NOCs), which could be found in the brain, have been verified as potent animal carcinogens and potential human carcinogens [2]. Maternal dietary exposure to NOCs or to their precursors during pregnancy has been found to be associated with childhood brain tumors [3]. It has been hypothesized dietary high exposure to NOCs increases adult glioma risk.

The precursors of the NOCs, nitrite and nitrate, are ubiquitous around us. Drinking water could be the primary source of nitrate exposure when the level is above maximum contaminant level (MCL) of 10 mg/L nitrate-nitrogen (nitrate-N). Below MCL, nitrate mainly comes from dietary, primarily vegetables [4]. About 5% of nitrate intake is endogenously converted to nitrite mainly by bacteria in the oral cavity [2, 5]. Nitrite intake mainly comes from processed meat, grain products and some vegetables [5]. Through a series of complex reaction in stomach, these precursors are converted to NOCs endogenously [6]. It is estimated that endogenous NOC formation accounts for 45-75% of total exposure to NOCs [7]. However, the results of previous studies on the relationship between dietary NOCs and risk of adult glioma have been inconsistent [8]. In addition, a meta-analysis of nine observational studies suggested a positive association of dietary NOCs intake from cured meats and the risk of adult glioma but the result was not certain and further studies were needed [9]. Thus, we suggest that nitrate and nitrite intake may play a role in adult glioma risk. Therefore, we conducted this meta-analysis to further investigate the associations between dietary nitrite and nitrate and the risk of adult glioma.

Materials and methods

Literature search

We conducted systematic searches in pubmed and embase using the terms “glioma” in combi-

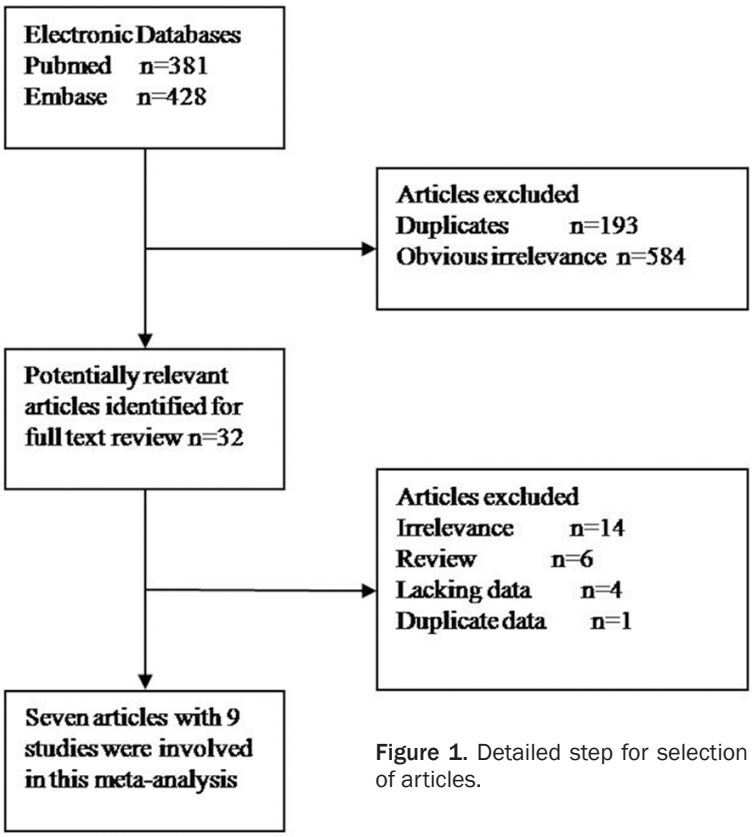

Figure 1. Detailed step for selection of articles.

nation with "*N*-nitroso compounds" or "nitrate" or "nitrite" or "nitrosamine" or "diet" or "dietary" or "lifestyle" or "cured meat" or "processed meat". Two investigators retrieved the literature and searched the articles independently.

Inclusion criteria

The included studies had to meet the following conditions: (1) applied a case-control or cohort design. (2) the exposure of interest was intake of nitrate and nitrite. (3) the outcome of interest was primary glioma which happened in adults (age ≥18). (4) the odds ratio (OR) or relative risk (RR) with 95% confidence interval (CI) were available. Meanwhile, we excluded the "reviews" and "repeated publications".

Data extraction

The following information was extracted from the studies we collected: name of the first author, year of publication, study design, study region, study participants sex and age range, the number of the cases, the OR or RR with corresponding 95% CI for the highest versus lowest level. Risk estimates adjusted for the greatest number of potential confounders were extracted from each study. Data extraction was conducted independently by three authors and disagreements were resolved by discussion with a third reviewer.

Statistical analysis

ORs and RRs with corresponding 95% CI were extracted from the studies included. Because the incidence of glioma was low, the RR was mathematically similar to the OR in the studies. Thus, all results were reported as OR for simplicity. The random- or fixed-effects model was used to quantify the relationship between nitrite or nitrate intake and the risk of adult glioma depending on the heterogeneity of the analysis [10]. The Q and I^2 statistics were used to evaluated the heterogeneity among the studies included [11]. 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 [12]. If heterogeneity existed, subgroup analysis was performed to assess variations in influence of these variables on overall results. Influence analyses were carried out to explore the substantial impact on between-study heterogeneity of each study. All analyses were performed by Stata 12.0. $P < 0.5$ was considered statistically significant.

Results

Search results and study characteristics

In accordance with the search strategy, 7 articles [13-19] with 9 studies (2 cohort studies and 7 case-control studies) involving 2264 adult glioma cases were enrolled in the meta-analysis of the association between nitrite intake and glioma risk. 6 studies were performed in USA, 2 in Australia and 1 in Germany.

Table 1. Characteristics of the studies involved

First author [ref], year, country	Study design	Age gender	Cases	OR (95% CI) for highest versus lowest category		Adjustment or matched
				Nitrite	Nitrate	
Boeing et al. [13] 1993 Germany	Case-control	25-75 Both	115	1.10 (0.60-2.00)	0.9 (0.5-1.5)	Age, sex, smoking, alcohol consumption
Giles et al. [14] 1994 Australia	Case-control	20-70 Both	409	1.58 (0.96-2.56) for males 0.98 (0.55-1.72) for females	1.13 (0.68-1.86) for males 0.53 (0.28-0.96) for females	Alcohol and tobacco intake
Blowers et al. [15] 1997 USA	Case-control	25-74 Female	91	1.40 (0.60-3.50)	0.70 (0.20-1.80)	Matched the patient on age (within five years) and race (Black or White)
Lee et al. [16] 1997 USA	Case-control	≥20 Both	434	1.18 (0.63-1.73) for males 1.56 (0.77-2.35) for females	_____	Adjusted for age (five-year age groups), gender, and race/ethnicity (White, Black, Hispanic, Asian, and other)
Chen et al. [17] 2002 USA	Case-control	≥21 Both	236	0.80 (0.50-1.30)	0.70 (0.40-1.20)	Adjusting for age, age squared, gender, total energy intake, respondent type, education level, family history, and farming experience
Michaud et al. [18] 2009 USA	Cohort	25-75 Both	335	1.26 (0.89, 1.79)	1.02 (0.66, 1.58)	Adjusted for age and caloric intake (quintiles)
Dubrow et al. [19] 2010 USA	Cohort	50-71 Both	585	1.32 (1.01-1.71)	1.28 (0.97-1.70)	Adjusted for sex, age, race, energy intake, education, height, and history of cancer at base line

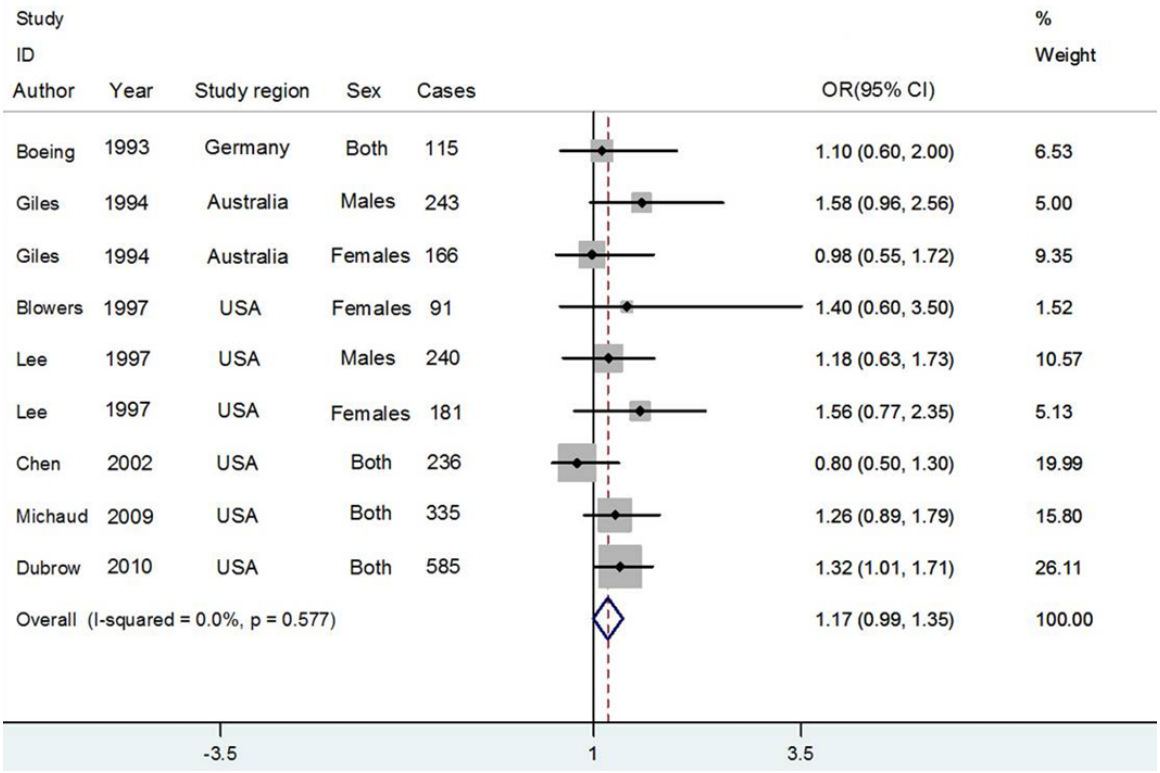

Figure 2. The forest plot between highest categories of nitrite intake and glioma risk. White diamond denotes the pooled OR. Black squares indicate the OR in each study, with square sizes inversely proportional to the standard error of the OR. Horizontal lines represent 95% CI.

Meanwhile, 6 articles with 7 studies (2 cohort studies and 5 case-control studies) involving 1771 cases about nitrate intake and adult glioma risk were used in this meta-analysis. 4 studies were conducted in USA, 2 in Australia and 1 in Germany. **Figure 1** shows the detailed step for selection of articles. **Table 1** gives the characteristics of the studies involved.

High versus low analyses

For nitrite intake and adult glioma risk, data from 7 articles with 9 studies including 2264 cases were used. The positive association of nitrite intake with the risk of adult glioma was reported in 1 study, and no significant association of nitrite intake with the risk of adult glioma was reported in 8 studies. Pooled results suggested that the highest nitrite intake versus the lowest level was not significantly associated with the risk of glioma (summary OR = 1.17, 95% CI = 0.99-1.35) with no heterogeneity (I^2 = 0.0%, P = 0.577). **Figure 2** shows the forest plot between highest categories of nitrite intake and glioma risk.

For nitrate intake and glioma risk, data from 6 articles with 7 studies including 1771 cases were used. Pooled results suggested that the highest nitrate intake versus the lowest level was not significantly associated with the risk of adult glioma (summary OR = 0.89, 95% CI = 0.66-1.12) with heterogeneity (I^2 = 44.0%, P = 0.098). **Figure 3** shows the forest plot between highest categories of nitrate intake and glioma risk.

Subgroup analysis and influence analysis

In the analyses of dietary nitrate and adult glioma risk, evidence of heterogeneity (I^2 = 44.0%, P = 0.098) was found in the pooled results. Subgroup analysis by study design and study region was performed. The association was significant in case-control studies (OR = 0.72, 95% CI = 0.52-0.93), but not in cohort studies (OR = 1.18, 95% CI = 0.89-1.47). No significant within group heterogeneity was observed in both case-control studies (I^2 = 0, P = 0.468) and cohort studies (I^2 = 0, P = 0.386). Thus, study design may play an important role in overall

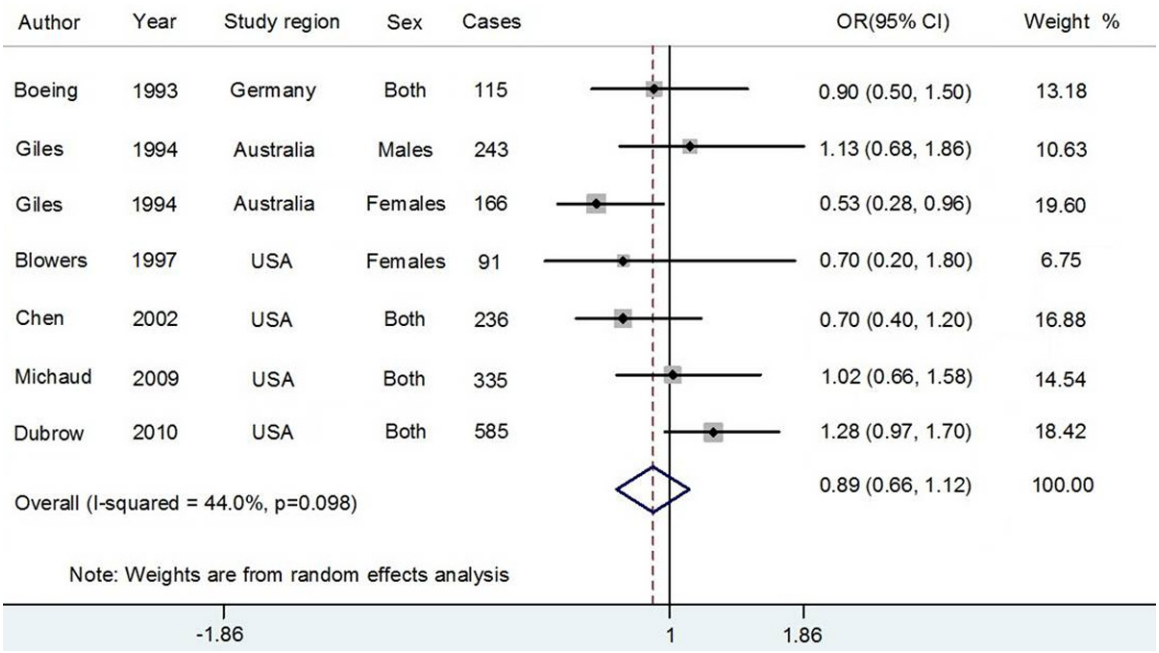

Figure 3. The forest plot between highest categories of nitrate intake and glioma risk. White diamond denotes the pooled OR. Black squares indicate the OR in each study, with square sizes inversely proportional to the standard error of the OR. Horizontal lines represent 95% CI.

Table 2. Subgroup analysis

Sub-groups	Cases	Studies	OR (95% CI)	I^2 (%)	P heterogeneity
All studies	1771	6			
Study design					
Case-control	851	4	0.72 (0.52-0.93)	0.0	0.468
Cohort	920	2	1.18 (0.89-1.47)	0.0	0.386
Study Region					
USA	1247	4	0.97 (0.67-1.27)	39.6	0.174
Others	524	2	0.79 (0.43-1.15)	43.4	0.171

heterogeneity. However, in the subgroup analyses of study region, when we restricted the analysis to USA and others, significant associations were found neither in studies performed in USA (OR = 0.97, 95% CI = 0.67-1.27) nor in studies performed in other countries (OR = 0.79, 95% CI = 0.43-1.15). The heterogeneities were detected both in the studies conducted in USA (I^2 = 39.6, P = 0.174) and in the studies conducted in other countries (I^2 = 43.4, P = 0.171). This suggests that study region may not be the cause of heterogeneity. The results of subgroup analyses are shown in **Table 2**.

Discussion

The result of this meta-analysis suggested that neither dietary nitrite nor nitrate was associated with glioma risk. No significant association was found in both case-control studies and cohort studies.

Positive association between cured meat or processed meat and adult glioma has been suggested by several studies [9, 13, 16]. However, when we calculate the total consumption of nitrite or nitrate, no consistent association with glioma risk is found. Thus, some other components in processed meat may account for the observed association. Conversely, positive association between intake of nitrite from plant sources, but not from animal sources, and glioma risk in males was found in Dubrow's study [19]. In addition, total exposure to NOCs, but not endogenous NOCs formed from nitrite and nitrate, may associated with glioma risk.

Heterogeneity exists in the study of dietary nitrate and the risk of glioma and may arise from publication year, study region, and study design. To explore the cause of heterogeneity, we conducted Subgroup analyses by the type of study design and study region. Study design was found to be a key contributor to the heterogeneity.

Nevertheless, the limitations exist in this meta-analysis. First, most studies included were case-control studies. Therefore, selection and recall bias may affect the results. More cohort studies are needed to the further investigation. Second, the data in the studies were obtained from questionnaires which only listed the food in dietary. But the questionnaires could not reflect the actual accurate data of intake of nitrite and nitrate. Besides, patients may change their dietary habits after diagnosis. Third, the data we combined was the highest category of nitrate/nitrite intake versus the lowest category and the dose-response analysis could not be performed because of limited data. Fourth, dietary antioxidants, including vitamin E and vitamin C intake, could inhibit the endogenous formation of NOCs from nitrite and nitrate, and therefore may be protective against glioma [2, 8, 20]. But nitrite and nitrate intake in combination with vitamin C and vitamin E intake is not analyzed in this study due to limited data. However, previous studies showed that vitamin E is not associated with glioma risk and vitamin C just might decrease the risk of glioma [21, 22].

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Disclosure of conflict of interest

None.

Address correspondence to: Dong Zhou, Department of Neurosurgery, Guangdong General Hospital, Guangdong Academy of Medical Sciences, No. 106, Zhongshan Second Road, Guangzhou 510008, Guangdong Province, P. R. China. Tel: 86-20-83827812-61521; E-mail: zhoudong5413@163.com

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