Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org
Original Research

Dietary fresh fish and processed fish intake and the risk of glioma: A meta-analysis of observational studies

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Received November 9, 2018; Accepted December 26, 2019; Published December 31, 2019

Doi: http://dx.doi.org/10.14715/cmb/2019.65.8.8

Abstract: The current study was to evaluate the predicted role of dietary fresh fish and processed fish intake for risk of glioma. Databases of Web of Science, PubMed, and Wan Fang Med Online were retrieved up to Jan 31th, 2018. Eligible studies were identified based on defined inclusion criteria. Summarized results of relative risk (RR) with corresponding 95% confidence intervals (CI) were calculated using a random effects model. Sensitivity analysis and publication bias were also performed. The final analysis in this report included a total of 9 articles. The summarized RR and 95%CI from 8 studies for dietary fresh fish intake and glioma risk was 0.823 (95%CI= 0.698-0.970), with no evidence of significant between-study heterogeneity (I^2=43.6%, P=0.088). Moreover, positive associations were also found both in Caucasian populations and Asia populations. Seven studies were used to assess the relationship between dietary processed fish intake and the risk of glioma. Significantly increased risk of glioma was found for the highest category of dietary processed fish intake [summarized RR= 1.554, 95%CI= 1.169-2.066, I^2= 72.1%, P= 0.001], especially among Caucasian populations. No publication bias was found. In summary, findings from this meta-analysis concluded that dietary fresh fish intake could reduce the risk of glioma. However, very high processed fish intake had a significant association with increased glioma risk.

Key words: Dietary. Fresh fish. Processed fish. Glioma. Meta-analysis.

Introduction

Glioma is a form of brain cancer. It is the most common tumour of the primary central nervous system and it has a relative poor prognosis (1, 2). However, its etiology and pathogenesis remains unclear. Publications data had shown that glioma in different regions had difference incidence rate (3). Furthermore, glioma accounts for about 50% of primary tumors of the central nervous system, and there is an upward trend (4, 5). Epidemiology studies have indicated that genetic factor is an established risk factor for glioma patients (6, 7). Furthermore, other potential risk factors include mobile phone use (8), allergy (9), smoking (10), diabetes mellitus (11), vitamins (12-14). Previous meta-analysis found that fish intake might be associated with lower risk of brain cancer risk (15). However, fresh fish and processed fish are different about its affect. Some publications articles have shown that dietary fish intake including fresh fish or processed fish may be a risk factor for glioma, but some differences were found between the results of the study. The objective of this meta-analysis was to explore the potential association between dietary fresh fish and processed fish intake and glioma risk. Between-study heterogeneity and publication bias were also explored in this meta-analysis.

Materials and Methods

Literature search

Studies were identified from the electronic databases of Web of Science, PubMed, and Wan Fang Med Online, with the strategy of ('fish' OR 'dietary') AND ('glioma' OR 'brain cancer' OR 'brain tumo(u)r' OR 'Central Nervous System tumo(u)r') up to Jan 31th, 2018. Moreover, the references of the retrieved articles were checked to identify additional studies. Two investigators independently conducted this systematic search.

Inclusion and exclusion criteria

The inclusion criteria for studies in this meta-analysis were as following: (1) studies were conducted with observational studies; (2) studies investigating the association between dietary fresh fish and/or processed fish intake and risk of glioma; (3) the relative risk (RR), odds ratio (OR), or hazard ratio (HR) with the corresponding 95% confidence interval (CI) in the relation was available, or could be calculated basing on relevant data; (4) human studies.

By contrast, the studies were excluded if they: (1) reported on animals studies; (2) was a review, letter to the editor or a comment.

Data extraction

The following required data were abstracted by two

independent individuals according to a predefined standardized form: the first author's last name; publication years; region for the study; study type; mean age or age range; cases and participants; type of fish (we summary the relationship between fresh fish or processed fish and glioma risk); RR or OR or HR with 95%CI for the association between dietary fish intake and glioma risk and adjustment for covariates. Disagreements were resolved through discussion.

Statistical analysis

Summarized RR with the corresponding 95% CI was used to calculate the summary results (16). Heterogeneity was evaluated with I^2 statistic (17), and defined as low (I^2< 25%), moderate (I^2= 25%-50%), or high (I^2> 50%) (18). A random effects model was used for this analysis. Sensitivity analysis was carried out to evaluate the potential effects of the individual study to the overall results when removed one single study. Potential publication bias was examined via the Begg's funnel plots (19) and Egger's test (20). All analyses were two sided, with P< 0.05 indicating statistical significance. The Stata 10.0 software was used to carry out the statistical analyses.

Results

Search results

Figure 1 shows the flow diagram of this study. The initial screening identified 563 articles from Web of Knowledge, 592 articles from PubMed and 89 articles from Wan Fang Med Online. After excluded the duplications from the different databases, 921 articles were reviewed for title and abstract. Thirty articles were further reviewed for full text. There are 21 articles were further excluded due to duplicate publications, OR or RR or HR not available, reviews or animal studies. The final analysis in this report includes a total of 9 articles (21-29).

Characteristics of studies

There were 9 articles suitable for this meta-analysis. Eight studies form 7 publications (21, 22, 25-29) were included for the analysis between dietary fresh fish intake and glioma risk. Seven studies from 5 publications (22-24, 26, 27) were conducted to assess the relationship between dietary processed fish intake and glioma risk. All of the studies were case-control studies. Five articles were population based case-control studies and 4 articles were hospital based case-control studies. Three articles came from United States, one from Germany, One from China, One from Australia, one from Israel, and two were Caucasian populations. All of the suitable studies included 2813 glioma cases and 7767 participants. Characteristics of the included studies are summarized in Table 1.

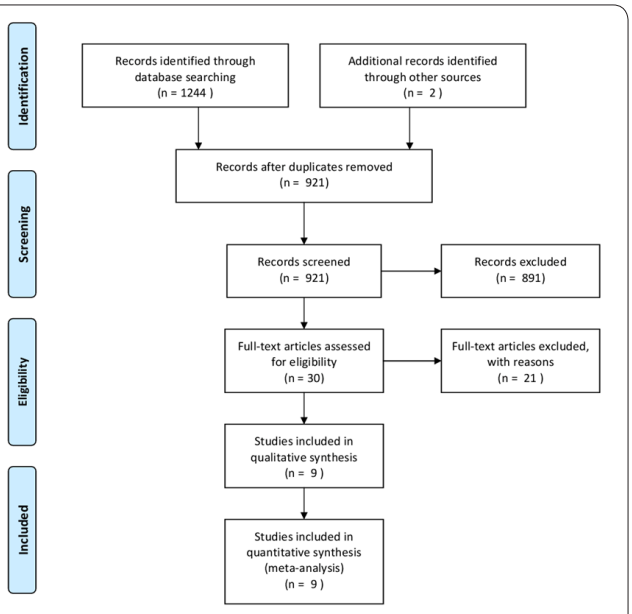

Figure 1. Study selection process for this meta-analysis.

Dietary fresh fish intake and glioma risk

Eight studies were conducted to assess the association between dietary fresh fish intake and glioma risk. Six studies reported a protection but non-significant association for glioma risk with highest dietary fresh fish intake, while only one study concluded a positive relation between dietary fresh fish intake and glioma risk. However, one study suggested that highest category of dietary fresh fish intake had an increased but non-significant association for glioma risk. The summarized RR for highest category of dietary fresh fish intake versus lowest intake was 0.823 (95%CI= 0.698-0.970). No significant heterogeneity was found (I^2=43.6%, P=0.088; Figure 2).

In the stratified analysis by sources of controls, inverse relationships were found both in population-based case-control studies (summarized RR=0.848, 95%CI= 0.710-0.983) and hospital-based case-control studies (summarized RR=0.686, 95%CI= 0.445-0.958). When we conducted the subgroup analysis by ethnicity, signi-

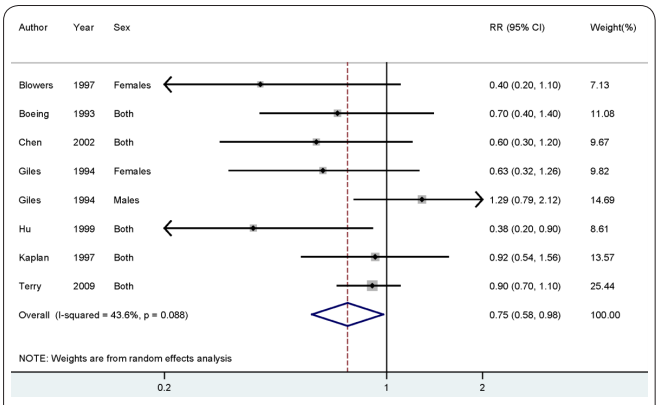

Figure 2. Forest plot of the association between dietary fresh fish intake and glioma risk.

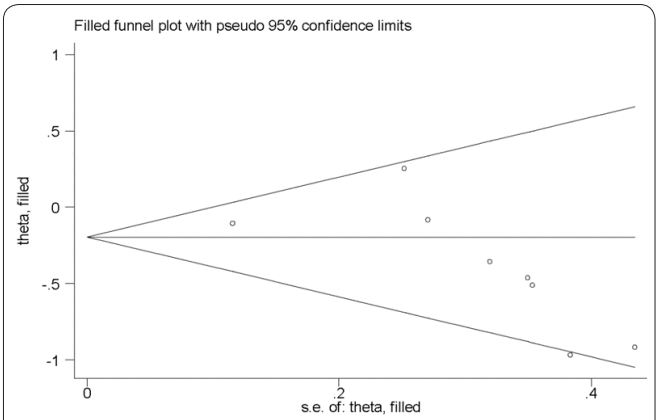

Figure 3. Funnel plot for assessment of publication bias.

Table 1. Characteristics of the included studies on fish consumption and glioma risk.

Study, year	Country	Study design	Participants (cases)	Age (years)	Type of fish	RR (95%CI) for highest versus lowest category	Adjustment for covariates
Blowers et al, 1997	United States	PCC	188 (94)	25-74	Fresh frozen fish	0.4(0.2-1.1)	Adjusted for age (within five years), gender and race (Black or White).
Boeing et al. 1993	Germany	PCC	533 (115)	25-75	Fish and processed fish	Fish 0.7(0.4-1.4) Processed fish 1.4(0.8-2.4)	Adjusted for age, gender, tobacco-smoking and alcohol consumption.
Bunin et al. 2006	United States and Canada	HCC	630 (315)	NA	Smoked fish or lox	1.3(0.6-2.6)	Adjusted for income level, mother's race, age of child at interview, date of interview, gained weight as a result of nausea/vomiting, number cigarettes per day, and total calories.
Burch et al. 1987	United States	HCC	430 (215)	25-80	Salt fish and smoke fish	Salt fish 1.40(0.44-4.41) Smoke fish 1.67(0.61-4.59)	Adjusted for sex, area of residence, marital status, year of birth z(within 5 yr), date of diagnosis (within 1 yr) for live cases, and date of death (within 1 yr) for dead cases.
Chen et al. 2002	United States	PCC	685 (236)	≥21	Fish	0.6(0.3-1.2)	Adjusting for age, age squared, gender, total energy intake, respondent type, education level, family history, and farming experience.
Giles et al. 1994	Australia	PCC	818 (409)	20-70	Fresh fish and processed fish	Fresh fish 1.29(0.79-2.12) for males 0.63(0.32-1.26) for females Processed fish 1.19(0.62-2.26) for males 1.44(0.77-2.66) for females	Adjusted for alcohol and tobacco.
Hu et al. 1999	China	HCC	331 (73)	20-74	Fresh fish and salted fish	Fresh fish 0.38(0.20-0.90) Salted fish 50.83(11.2-230.9)	Adjusted for income, education, cigarette smoking, alcohol intake, selected occupational exposures and total energy intake.
Kaplan et al. 1997	Israel	HCC	417 (139)	18-75	Fish	0.92(0.54-1.56)	Adjusted for age, sex and ethnic origin.
Terry et al. 2009	Caucasian	PCC	3671 (1185)	20-80	Fresh fish	0.9(0.7-1.1)	Adjusted for age, sex, center and the following food groups: leafy green vegetables, yellow-orange vegetables, cured meat, non-cured meat, fresh fish, dairy eggs, grains, and citrus fruit.

Abbreviations: RR= relative risk; CI= confidence interval; NA= not available; PCC= Population-based case-control studies; HCC= Hospital-based case-control studies.

Table 2. Summary risk estimates of the association between fresh fish or processed fish intake and glioma risk.

Sub-groups	Fresh fish				Processed fish			
	Studies, n	RR(95%CI)	I^2 (%)	$P_{heterogeneity}$	Studies, n	RR(95%CI)	I^2 (%)	$P_{heterogeneity}$
All studies	8	0.823(0.698-0.970)	43.6	0.088	7	1.554(1.169-2.066)	72.1	0.001
Sources of control								
Population-based	6	0.848(0.710-0.983)	38.0	0.153	3	1.348(0.953-1.907)	0.0	0.903
Hospital-based	2	0.686(0.445-0.958)	71.8	0.060	4	2.084(1.267-3.429)	84.5	0.000
Ethnicity								
Caucasian	6	0.848(0.710-0.983)	38.0	0.153	6	1.367(1.023-1.827)	0.0	0.996
Asia	2	0.686(0.445-0.958)	71.8	0.060	1	-	-	-
Number of cases								
<200	5	0.635(0.472-0.855)	18.2	0.299	5	1.752(1.233-2.491)	80.2	0.000
≥200	3	0.922(0.757-1.123)	39.4	0.192	2	1.237(0.762-2.009)	0.0	0.859

ficant associations were also found both among Caucasian populations (summarized RR=0.848, 95%CI= 0.710-0.983) and Asia populations (summarized RR=0.686, 95%CI= 0.445-0.958). Although the association was not significant in the subgroup analysis of number of cases ≥200, positive relationship was found in the group of those cases <200. Detailed results are showed in Table 2.

Begg's funnel plots (Figure 3) and Egger's test (P= 0.172) indicated that no publication was found in the analysis. Sensitivity analysis showed that there is no single study had potential effects on the whole result while removed a single study at time (Figure 4).

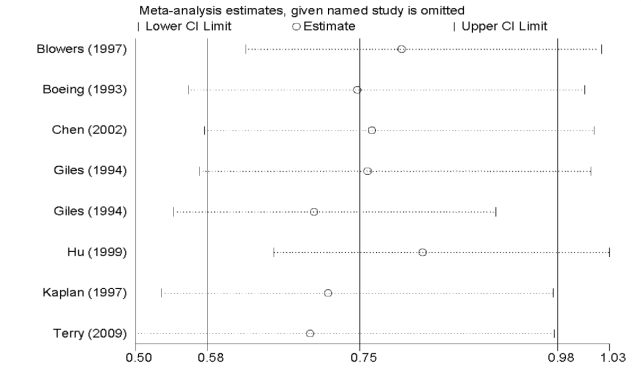

Figure 4. Sensitivity analyses for assessment of association between dietary fresh fish intake and glioma risk.

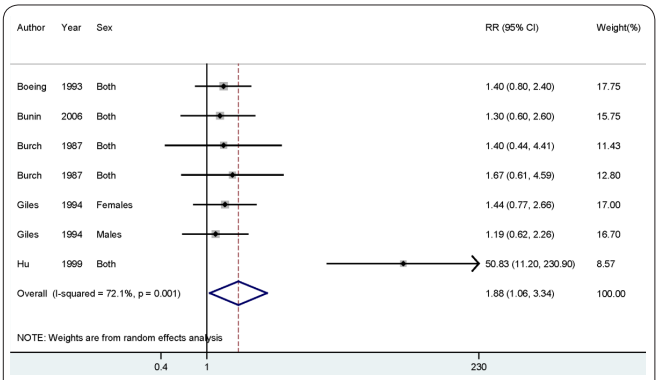

Figure 5. Forest plot of the association between dietary processed fish intake and glioma risk.

Dietary processed fish intake and glioma risk

Seven studies from 5 publications were included to investigate the association between dietary processed fish intake and glioma. Six of the included studies reported a non-significant association between them, while one study suggested that highest category of dietary processed fish intake could increase the risk of glioma. Pooled result indicated that highest category of dietary processed versus lowest category could significantly increase glioma risk [summarized RR= 1.554, 95%CI= 1.169-2.066]. Evidence of between-study heterogeneity was found (I^2= 72.1%, P= 0.001; Figure 5).

Upon a stratified analysis based on sources of controls, we found significant association in the subgroup analysis of population-based case-control studies (summarized RR= 1.138, 95%CI= 1.013-1.677) and hospital-based case-control studies (summarized RR= 2.084, 95%CI= 1.267-3.429). Six of the included studies were Caucasian populations, and the relation was significant (summarized RR= 1.367, 95%CI= 1.023-1.827). The association was not significant in the subgroup analysis of number of cases ≥200, but positive relationship was found in the group of those cases <200.

Egger's test (P= 0.209) indicated that no publication was found in the report. Sensitivity analysis showed that there is no study had potential effects to the whole result when removed a study at time. Detailed results are showed in Table 2.

Discussion

The overall analyses concluded that highest category of dietary fresh fish intake could significantly reduce the risk of glioma. Positive associations were also found both among Caucasian populations and Asian populations. However, findings from 7 independent studies showed that highest levels versus lowest levels of dietary processed fish intake could increase the glioma risk. Significant association was also found among Caucasian populations. Sensitivity analysis showed that there is no single study had potential effects to the whole result when removed a study at time. Publication bias was not found either in dietary fresh fish intake group or in dietary processed fish intake group.

In our meta-analysis, we found high between-study heterogeneity on the association between dietary processed fish intake and glioma risk. A paper had said that between-study heterogeneity in the meta-analysis is common (30), and it is an essential component to explore the heterogeneity existed in the between-study. Meta-regression was used to explore the causes of

heterogeneity. However, we did not find any covariate having a significant impact on between-study heterogeneity. Subgroup analyses by sources of control, ethnicity and number of cases were also performed. And between-study heterogeneity persisted in some of the subgroups, suggesting the presence of other unknown confounding factors.

Previous studies had indicated that high levels of processed meat consumption might increase the risk for glioma (31). In our report, we also obtained a positive association between highest categories of dietary processed fish intake and glioma risk. The experimental neurocarcinogenicity of N-nitroso compounds (NOC) had been reported under differing laboratory conditions and in a wide variety of animal species (32, 33). Processed fish had been used as markers of N-nitroso compounds exposure. Furthermore, the salt content of processed fish and the potential effect of different cooking/preparation methods on carcinogenic risk should also be considered. Many epidemiological studies and reviews have found that consumption of highly salted food was strongly associated with the risk of carcinogenesis (22). 2-chloro-4-methylthiobutanoic acid is also a mutagen present in salted fish (34). Chemical carcinogens such as nitrites and heterocyclic amines have been detected in fish cooked by grilling at high temperatures. Therefore, it may be a risk factor for glioma risk. However, co-occurrence of vitamin E in fresh fish effectively blocks the formation of NOC. This may be the reason for reduced glioma risk with highest levels of dietary fresh fish intake.

Some potential limitations in this study were required attention. Firstly, only English articles were included, which may omit other languages studies. However, no publication bias was found. Secondly, only case-control studies were included. The retrospective nature of case-control studies and the possibility of bias and confounding factors cannot be excluded; for example, some subjects may have modified their fish eating habits after the baseline assessment. However, case-control design was a very important epidemiological approach in the observational study. Thirdly, evidence of high heterogeneity was observed in the whole pooled result and some subgroups, which could not be avoided because of the confounding factors from original studies. Fourth, we did not obtain a positive relation between fresh fish intake and processed fish intake and glioma risk in the subgroup analysis of number of cases ≥200, probably due to the little studies and little cases included. Finally, the methods and units of measuring fish intake also differed amongst the various studies. This may produce the between-study heterogeneity.

In summary, findings from this meta-analysis concluded that dietary fresh fish intake could reduce the risk of glioma, both among Caucasian populations and Asian populations. However, highest category of processed fish intake might increase the risk of glioma, especially among Caucasian populations.

Acknowledge
None.

Funding
None.

Competing interests
None.

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