Tumor Biol. (2014) 35:3875–3880
DOI 10.1007/s13277-013-1514-4

RESEARCH ARTICLE

Allergic conditions reduce the risk of glioma: a meta-analysis based on 128,936 subjects

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Received: 3 November 2013 / Accepted: 3 December 2013 / Published online: 18 December 2013

Abstract Many studies have investigated the association between the allergic conditions and the risk of glioma. However, the evidence is inadequate to draw robust conclusions because most studies were generally small and conducted in heterogeneous populations. To shed light on these inconclusive findings, we conducted a meta-analysis of studies relating the allergic conditions to the risk of glioma. We identified the relevant studies by searching ISI Web of Science, PubMed, EMBASE, Chinese National Knowledge Infrastructure (CNKI) databases, and Wanfang database by October 2013. We included studies that reported odds ratio (OR) or hazard ratio (HR) with its 95 % confidence interval (CI) for the association between the allergic condition and the risk of glioma. Eighteen independent publications, with 9,986 glioma cases and 118,950 controls, were included. Our results showed that allergic condition was reversely associated with the risk of glioma (OR=0.78, 95 % CI 0.73–0.83, $P<0.001$). The results of our meta-analysis indicated that allergic conditions significantly reduce the risk of glioma.

Keywords Meta-analysis · Glioma · Allergy

Introduction

Glioma is the most common type of brain tumor worldwide [1]. The incidence rate of glioma is about six per 100,000 annually [1–3], and the 5-year survival rate is about 20 % [3,4]. However, little is known about the factors that lead to the development of glioma. Exposure to ionizing radiation [5,6], genetic polymorphisms [7–10], and history of a familial cancer such as Li–Fraumeni or Turcot syndrome are well-recognized risk factors, but they explain only a very small proportion of glioma cases. Recently, allergy has been consistently shown to be related to glioma risk [11–28]. Allergy consists of a group of heterogeneous diseases with different underlying mechanisms. However, common allergies including eczema, hay fever, and allergic asthma, characterized by immediate hypersensitivity reactions, are mediated by IgE, which is produced and regulated by the B cells as well as T helper type 2 (Th2) and type 17 (Th17) cells [28–30]. And the level of IgE was also found to be associated with the risk of glioma [31–34]. The glioblastoma patients with elevated IgE had 9 months longer survival than those with normal or borderline IgE levels [31]. In addition, allergy related genetic polymorphisms, such as IL-4R and IL-13 were also reported to be associated with the risk of glioma [35]. These evidences indicated that allergic conditions were associated with glioma. Since the relatively small sample size of a single study may not have enough power to detect slight effects of allergic condition on glioma, meta-analysis may provide more credible evidence by systematically summarizing existed data. Although two meta-analysis [36,37] reports analyzing the relation between allergic conditions and the incidence of glioma had been performed in 2007 and in 2011, respectively, there were several large case-control studies have been published since then [24–28]. In addition, the reported associations have remained inconsistent. Therefore, in this study we have extensively reviewed literature and performed a meta-analysis based on all eligible case-control published data to evaluate the association between allergic conditions and glioma risk.

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Materials and methods

Literature search and selection

We carried out a publication search in ISI Web of Science, PubMed, EMBASE, Wanfang database in China, and Chinese National Knowledge Infrastructure (CNKI) databases to identify relevant citations published between January 1979 and October 2013 with the following search terms: "brain tumor", "glioma", "allergy", "atopy", "asthma", "eczema", and "hay fever" by two independent investigators. Publication language was not restricted in our search. Abstract, review or editorials were not included. The references of all identified publications were searched for any additional studies, and the related articles option was used to search for further potentially relevant articles. Studies included in our meta-analysis have to meet the following criteria: (1) case-control or cohort studies investigating the association between allergic conditions and glioma; (2) cases were medically confirmed of glioma; (3) sufficient data for examining an odds ratio (OR) with 95 % confidence interval (CI).

Data extraction

Two investigators independently extracted data and reached a consensus on all of the items. For each study, the following characteristics were collected: the first author's last name, year of publication, country of origin, numbers of cases and controls.

Statistical analysis

Meta-analysis was performed by using RevMan 5.0 software provided by the Cochrane Collaboration (Oxford, UK). We directly used Q-test and I^2 test to examine the heterogeneity between each study. By heterogeneity test, if $P>0.05$, we select the Fixed Effect Mode1, and if $P<0.05$, we select the Random Effect Mode1 to merge OR. Analysis of sensitivity includes the difference of point estimation and CIs of the combined effects value at a different model, to observe whether it changes the result. To test the publication bias, we used the RevMan 5.0 statistical software to make the funnel plot. The statistical significance of the pooled OR was determined with the Z test, and a P value of <0.05 was considered significant.

Results

Literature search

A flow diagram of the literature search is shown in Fig. 1. Total searches yielded 342 entries. Of these, 301 studies were excluded after reading the title or abstract because of obvious irrelevance to our study aim. Forty-one studies appeared to be potentially relevant for inclusion in our study. Fifteen studies were excluded because of overlapping cases or their data were not extractable. A total of 26 full-text articles were reviewed. Eight studies were further excluded for no control population. Therefore, a total of 18 articles included 17 case-control studies [11–16,18–28] and three cohort studies [17] met the inclusion criteria.

Study characteristics

The characteristics including author information, publication year, number of cases and controls, and OR values and 95 % CIs of included studies were summarized in Table 1. These 18 included studies were published between 1990 and 2013 and comprised a total of 9,986 stroke cases and 118,950 control subjects.

Meta-analysis

An assessment of heterogeneity of 20 studies included for the analysis indicated that the hypothesis of homogeneity could not be accepted ($\chi^2=54.43$, $I^2=65$ %, $P<0.001$); therefore, the random-effects model was used to calculate the summary OR. As shown in Fig. 2, the ORs ranged from 0.55 to 1.04 amongst these studies. In the pooled analysis, our results showed that allergic condition was inversely associated with the risk of glioma (OR=0.78, 95 % CI 0.73–0.83, $P<0.001$).

Test of sensitivity

For the sensitivity analysis, we deleted one single study from the overall pooled analysis each time to check the influence of the removed data set to the overall ORs. The pooled ORs and 95 % CIs were not significantly altered when any part of the study was omitted, which indicated that any single study had little impact on the overall ORs.

Publication bias

Funnel plot and Egger's test were performed to assess the publication bias of the literature. Egger's test further confirmed the absence of publication bias in this meta-analysis ($P>0.05$) (Fig. 3).

Discussion

In this meta-analysis, we found an inverse association of allergic condition with the risk of glioma. The results demonstrated that allergic conditions significantly reduce the risk for developing glioma.

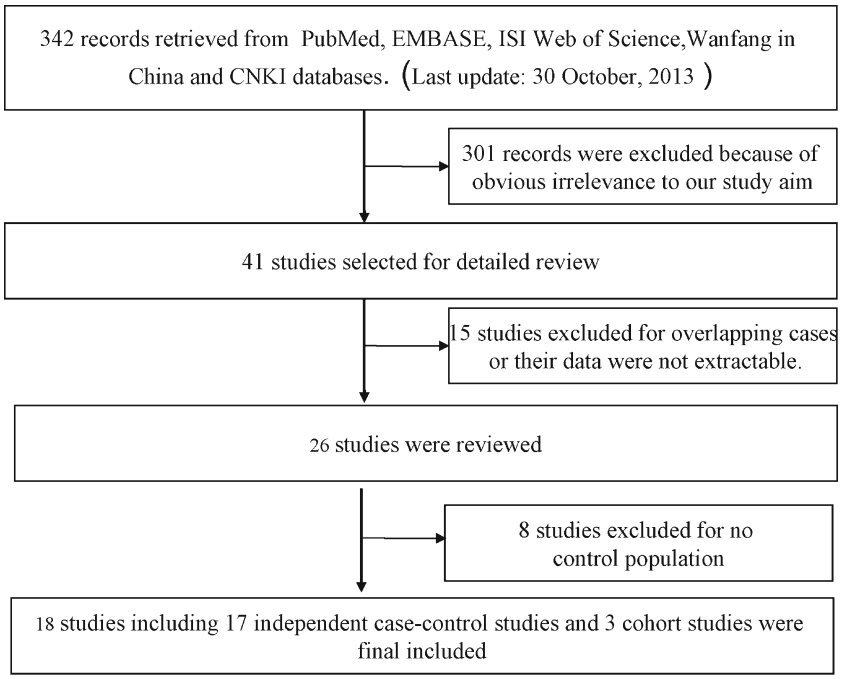

Fig. 1 Flow diagram of study identification

The possible role of allergic conditions in the development of glioma remains poorly understand. Allergy consists of a group of heterogeneous diseases with different underlying mechanisms. However, common allergies including eczema, hay fever, and allergic asthma, characterized by immediate hypersensitivity reactions, are mediated by IgE, which is produced and regulated by the B cells as well as T helper type 2 (Th2) and type 17 (Th17) cells [33,34]. The level of IgE may be a better marker to detect the relation between allergy and glioma because it is not affected by individual recall and

Table 1 The characteristics of included studies

Authors	Publication year	Country	Case	Control	OR (HR) 95%CI
Hochberg et al.	1990	United States	160	128	0.6 (0.4–1.0)
Ryan et al.	1992	Australia	110	416	0.54 (0.33–0.89)
Schlehofer et al.	1992	Germany	226	418	0.7 (0.5–1.0)
Cicuttini et al.	1997	Australia	416	422	0.8 (0.5–1.4)
Schlehofer et al.	1999	Six countries	1,178	1,987	0.59 (0.49–0.71)
Wiemels et al.	2002	United States	405	402	0.47 (0.33–0.67)
Schwartzbaum et al.	2003	Sweden	37	14,535	0.45 (0.19–1.07)
Schwartzbaum et al.	2003	Sweden	42	29,573	1.09 (0.48–2.48)
Schwartzbaum et al.	2003	Sweden	68	52,067	0.46 (0.14–1.48)
Schoemaker et al.	2006	United Kingdom	965	1,716	0.63 (0.53–0.76)
Schwartzbaum et al.	2007	Four countries	565	2,951	0.66 (0.54–0.80)
Wigertz et al.	2007	Five countries	1,527	3,309	0.70 (0.61–0.80)
Scheurer et al.	2008	United States	325	600	0.34 (0.23, 0.51)
Berg-Beckhoff et al.	2009	Germany	366	1,494	0.92 (0.70–1.22)
Wiemels et al.	2009	United States	535	532	0.50 (0.36–0.70)
Lachance et al.	2011	United States	855	1,160	0.4 (0.48–0.58)
McCarthy et al.	2011	United States	419	612	0.66 (0.49–0.87)
Lee et al.	2013	Korea	143	131	0.26 (0.12–0.58)
Safaeian et al.	2013	United States	851	3,977	0.71 (0.55–0.91)
Turner et al.	2013	Five countries	793	2,520	0.73 (0.60–0.88)

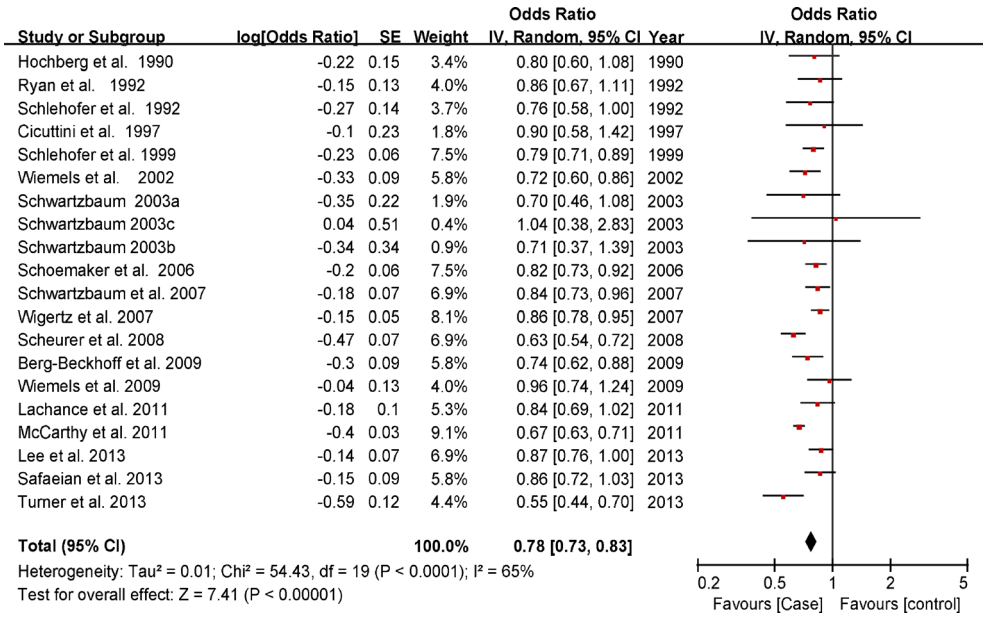

Fig. 2 Forest plot of allergic condition and glioma, the horizontal lines correspond to the study-specific OR and 95 % CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95 % CI. In this analysis, random-effects model was used

reporting. Schwartzbaum et al. [29] reported an inverse association between IgE levels and risk of glioma; the association was present at least 20 years before tumor diagnosis.

The protective role of allergic condition in the development of glioma is also supported by an association between germ line polymorphism and risk of glioma. SNPs and haplotypes in genes encoding IL-4, IL-4R, IL-13 critical for allergy and IgE production are the most intensely studied [35,38,39]. In our meta-analysis, we found the allergic conditions may reduce risk of glioma by 28.0 %. Our result was in line with previous studies. Previously, two meta-analysis [36,37] have reported the relation between allergic conditions and glioma risk. Linos et al. [37] enrolled eight studies with a total of 3,450 patients diagnosed with glioma and 1,070 patients with meningioma. The authors found the pooled relative risks (RRs) of glioma comparing those with a history of an atopic condition with those with no history of that condition were 0.61 (95 % CI, 0.55–0.67) for allergy. In 2011, Chen et al. [36] selected 12 studies to perform a meta-analysis involving 61,090 participants and found that the pooled OR with any allergic conditions for glioma was 0.60 (95 % CI, 0.52–0.69; $P<0.001$) which suggesting a significant negative association (protective effect) between allergy and glioma. In the present study, we included 20 studies including 9,986 glioma cases and 118,950 controls and demonstrated this reverse relation between glioma and allergy.

In addition, exploring heterogeneity is one of the important goals of meta-analysis. In this study we found significant heterogeneity among the included studies. Therefore, we utilized the randomly model to merge the OR value. Sensitivity analysis showed that omission of any single study did not have significant impact on the combined ORs. Furthermore, funnel plot did not reflect obvious asymmetry, and Egger's test further indicated no considerable publication bias in this meta-

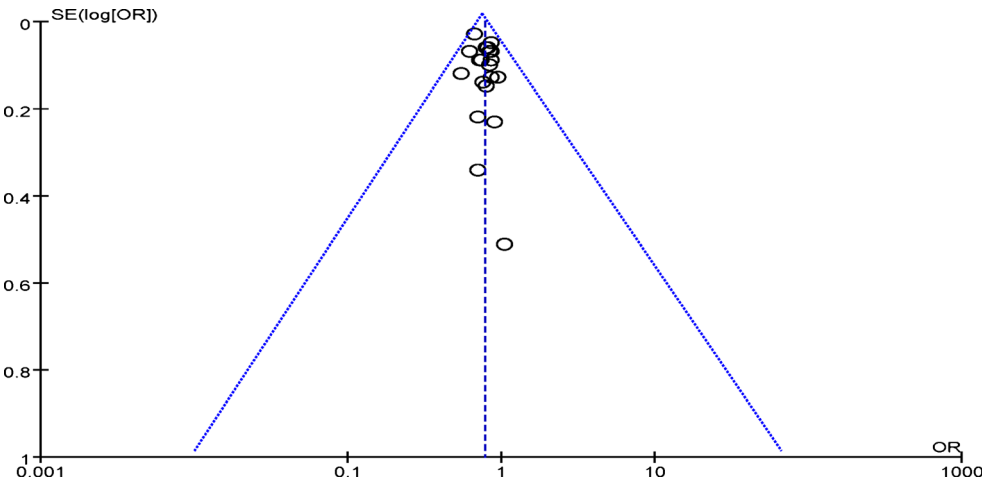

Fig. 3 Begg's funnel plot for publication bias tests. Each *point* represents a separate study for the indicated association. Log OR represents natural logarithm of OR. *Vertical line* represents the mean effects size

analysis. This made the results of this meta-study more reliable to some extent.

This study has several limitations including the methods of included studies were not the same one. And not all the studies defined the allergy by detecting the IgE level. Moreover, other clinical factors such as age, sex and different chemotherapies in each study might lead to bias. Determining whether or not these factors influence the results of this meta-analysis would need further investigation.

In conclusion, our study suggested that allergic condition was associated with a significantly decreased risk of glioma. Larger well-designed epidemiological studies with ethnically diverse populations and functional evaluations are warranted to confirm our findings.

Acknowledgments This work was supported by National Natural Science Foundation grant from China National Science Foundation Committee (No: 81172410).

Conflicts of interest None

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