Int J Clin Exp Med 2013;6(9):757-765
www.ijcem.com /ISSN:1940-5901/IJCEM1308007

Original Article

Personal hair dyes use and risk of glioma: a meta-analysis

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Received August 5, 2013; Accepted September 12, 2013; Epub September 25, 2013; Published September 30, 2013

Abstract: Background and Objective: Use of hair dyes for glioma risk has been investigated in numerous epidemiological studies, but the evidence is inconsistent. Therefore, a meta-analysis was performed to estimate the association between hair dyes use and glioma risk. Methods: We searched PubMed and EMBASE databases without any limitations, covering all papers published by the end of March 8, 2013. Cohort and case-control studies reporting relative risk estimates (RRs) with corresponding 95% confidence intervals (CIs) (or data to calculate them) on this issue were included. Random effects models were used to calculate the pooled RRs and corresponding 95% CIs. Results: Four case-control and two cohort studies were included in this meta-analysis. The summary RRs and 95 % CIs for ever users of any hair dyes were 1.132 (0.887-1.446) for all studies, 1.291 (0.938-1.777) for case-control studies, and 0.903 (0.774-1.054) for cohort studies. In the subgroup analysis by geographic regions and sex, the similar results were detected. No significant associations were also observed among the studies which reported data involving permanent hair dye use and duration of any hair dye use. Conclusion: In summary, the results of our study demonstrated that hair dyes use is not associated with risk of glioma.

Keywords: Glioma, hair dyes, risk factor, meta-analysis

Introduction

Glioma is the most commonly diagnosed type of brain tumors accounting for about 70% of cases [1]. The etiology of glioma is poorly understood. Ionizing radiation and some rare hereditary syndromes have been demonstrated to be well-established risk factors for glioma [1]. However, they could account for a small number of gliomas, since the two exposures were rare. In addition, other potential risk factors including dietary and other exposures to N-nitroso compounds, occupational exposures, hormonal factors, mobile phone use, head trauma, genetic polymorphisms, and chemical exposures, have been widely studied, but no clear conclusions have been drawn at present [2-7].

Hair dye is used widely in developed counties. Indeed, it has been estimated that about one-third of women over age 18 and 10% of men above age 40 in North America and Europe use any type of hair dye [8]. However, components of hair dyes including aromatic amines and related nitro-compounds have been found to be mutagenic in vitro and carcinogenic in animal experiments [9-11]. Therefore, hair dye could have a significant impact on public health. In recent years, a great number of studies investigated the relationship between hair dyes use and risk of glioma [12-18]. In a previous meta-analysis, Takkouche and colleagues found that hair dyes use is associated with increased risk of brain tumor [19]. Since then, five studies have confirmed or refused that finding [14-18]. Moreover, only two studies [12, 13] were included in Takkouche and colleagues' study [19]. Given that the result of previous meta-analysis may be observed by chance, an updated meta-analysis was performed to provide a more comprehensive and precise conclusion. Specifically, in our study, we (1) included all eligible studies, (2) analyzed data for any hair dye use and permanent hair dye, (3) analyzed data stratified by study design, geographic regions, and gender, (4) analyzed data by duration.

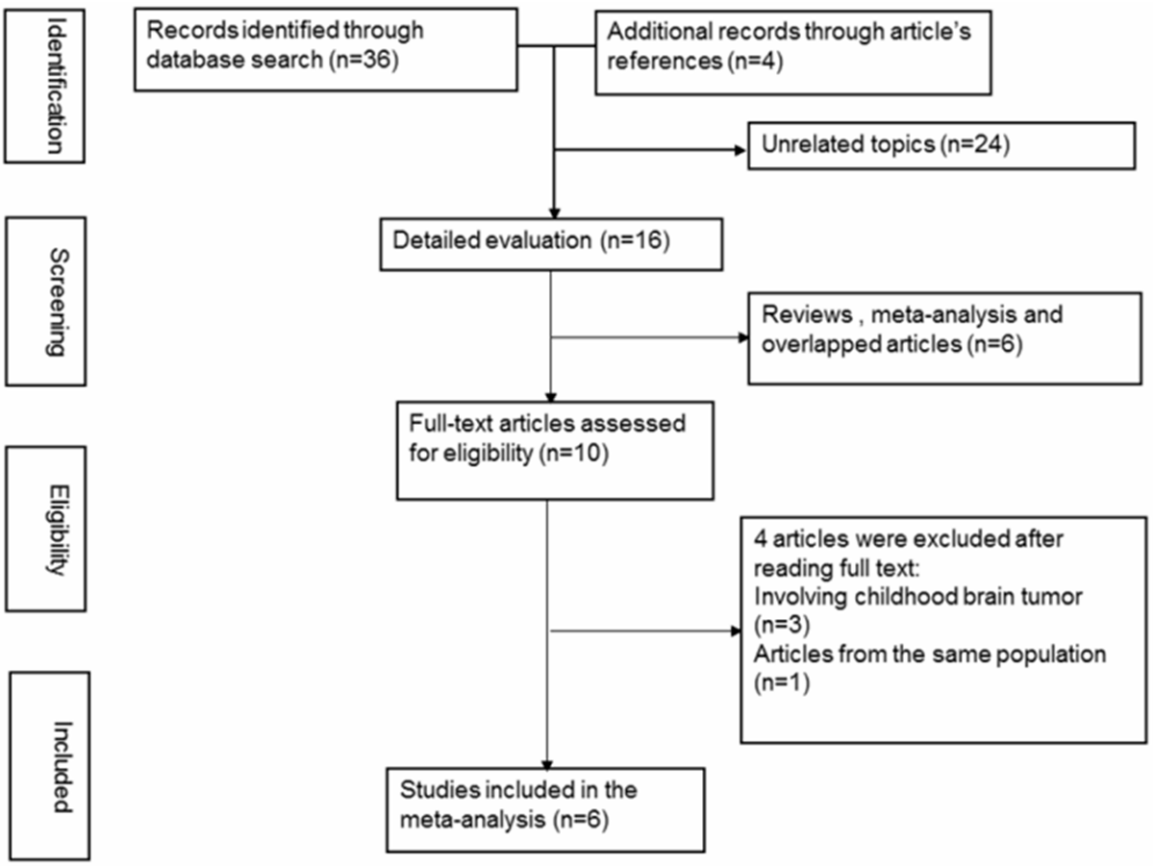

Figure 1. Flow diagram of t literature search and selection.

Methods

Literature search

We searched the electronic databases PubMed and EMBASE with using combinations of search terms such as hair dyes, hair color, glioma, brain tumors, brain cancer, and brain neoplasm. We also scanned the references of identified articles and reviews on this topic. Any limitations were not imposed. Searches were conducted independently by two reviewers (CS and ZYQ), and the latest search was conducted on March 8, 2013.

Inclusion criteria and exclusion criteria

We applied the following inclusion criteria: (1) original cohort and case-control studies; (2) assess the association between hair dyes use and risk of glioma, but at least brain tumor; (3) provide odd ratio (OR), or RR with corresponding 95% CIs or sufficient data (the distribution of cases and non-cases) to calculate them; (4) when multiple reports were published on the same study population, we selected the most comprehensive publication. In this study, we exclude those studies that concerned occupational exposure to hair dyes or involved childhood brain tumors related to use of hair dye by the mother.

Data collection

The following information was extracted independently from each eligible study by two authors: the first author's last name, year of publication, country in which conducted, study period/follow-up period, age of subjects, study design, number of cases/controls (cohort), percentage of study participants who reported exposure by proxy, methods of data collection, diagnostic criteria, and matching and adjustment. Any conflicting evaluations were resolved by discussion.

Statistical analysis

The RR was used as the common measure of association across studies. ORs were deemed

Table 1. Characteristics of the six studies included in the meta-analysis

First author, Publication year	Country in which conducted	Study Period/ Follow-up	Age (years)	Study design	Cases/ Controls	% Proxy reporting of cases (controls)	Methods of data collection[a]	diagnostic criteria	Matching or adjustment
Ahlbom, 1986	Sweden	1980-1981	20-75	PCC	78/92	29.5% (NA)	1, 3	medical records	Age, sex, and place of residence
Burch, 1987	Canada	1977-1981	25-80	HCC	215/215	NA	2	Histological diagnosis	Age, sex, place of residence, marital status, and diagnosis date
Altekruse, 1999	USA	1982-1994/7-12	≥ 30	Cohort	613/547,586	NA	3	International Classification of Diseases	Age, sex, race, cigarettes smoked per day (current smokers) or age at quitting (former smokers), education and blue-collar occupation.
Heineman, 2005	USA	1998-1993	≥ 21	PCC	112/215	79.0% (NA)	1	Histological diagnosis	Age, sex, race, education.
Bluhm, 2007	USA	1994-1998	18-99	HCC	782/799	18% (3%)	3	Histological diagnosis	Age, sex, race, hospital, distance from residence to the hospital, marital status, and educational attainment
Mendelsohn, 2009	China	1996-2000/7 (average)	40-70	Cohort	39/70,336	NA	2, 3	medical records	Age, sex, education, and smoking duration in pack/years

PCC, population-based case-control study; HCC, hospital-based case-control study; NA, data not available. [a]The methods of data collection are: (1) telephone interview, (2) in-person interview, (3) questionnaire.

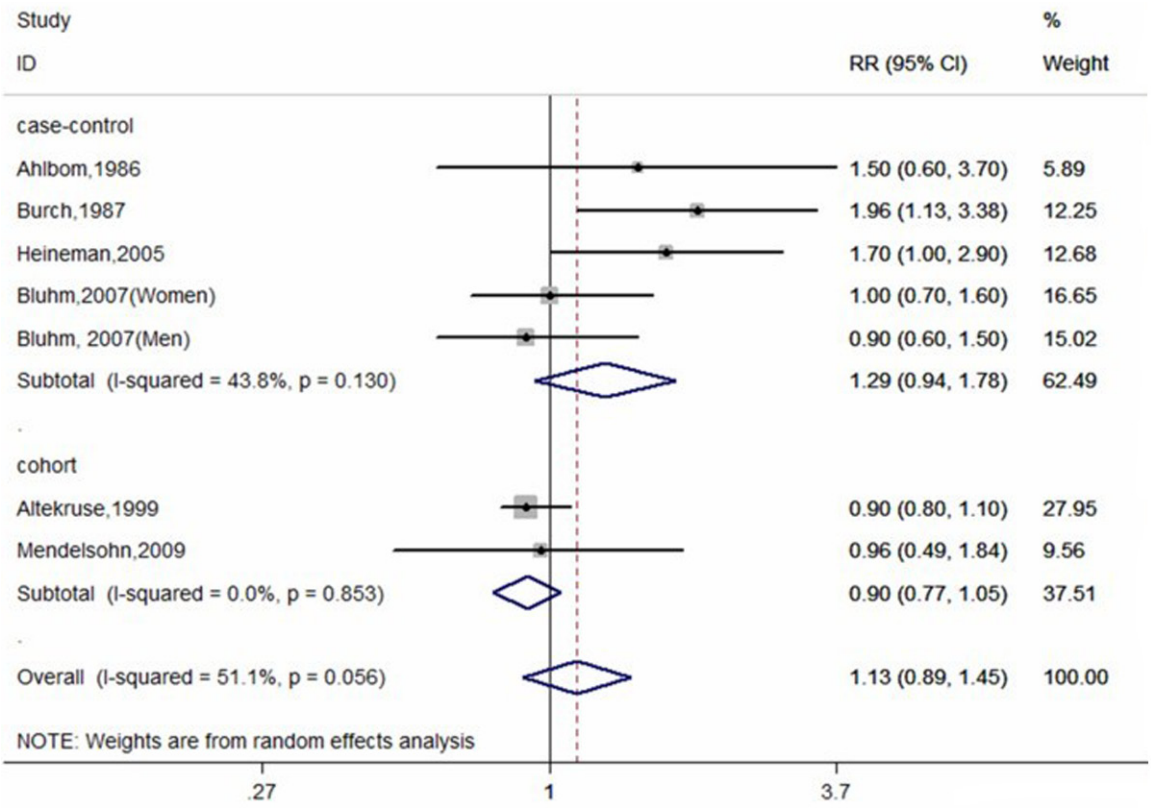

Figure 2. Forest plot of risk estimates of the association between any hair dyes use and risk of glioma.

equivalent to RRs because glioma is rare [20]. The most-adjusted risk estimates were included in the meta-analyses; however, when unavailable, the raw data were used. In one study [17] where the results were reported for women and men separately, we treated these results as previously [21]. In another study [16] where results on duration of hair dyes use were reported stratified by type of hair dyes (permanent and non-permanent), we combined them using the method proposed by Hamling et al [22] to calculate a total estimate for duration of any hair dye use. This method was used to combine estimates using the same reference category or the same set of controls, taking into account correlation between estimates. For one study [12], we excluded the data of the 'clinical' control group, since it included a subgroup of subjects with meningioma, pituitary adenoma, or cerebral aneurysm.

All the meta-analytic estimates were computed from random-effect model, which considers both within-study and between-study variation [23]. Heterogeneity across studies was evaluated by Q statistic and I^2 statistic [24, 25]. Significant heterogeneity was defined as a P value < 0.10 [24]. Sensitivity analysis and publication bias analysis were performed to assess the stability of the results as previously [26, 27]. Briefly, sensitivity analyses were performed to investigate the influence of a single study on the overall risk estimate by excluding one study in each turn. Publication bias was assessed by Egger's test ($P < 0.05$ indicated the presence of potential publication bias) [28]. As the most common definition of exposure among the included studies was ''any hair dyes users versus non users", this was chosen to be the focus of the main analysis. Subgroup analyses were also performed according to study design and geographic regions. Geographic distribution of all included studies was 3 in USA, 1 in Canada, 1 in China, and 1 in Sweden. Therefore, geographic regions were categorized into two groups: USA and other countries.

All statistical analyses were conducted with the STATA software, version 11.0 (STATA Corporation, College Station, TX, USA).

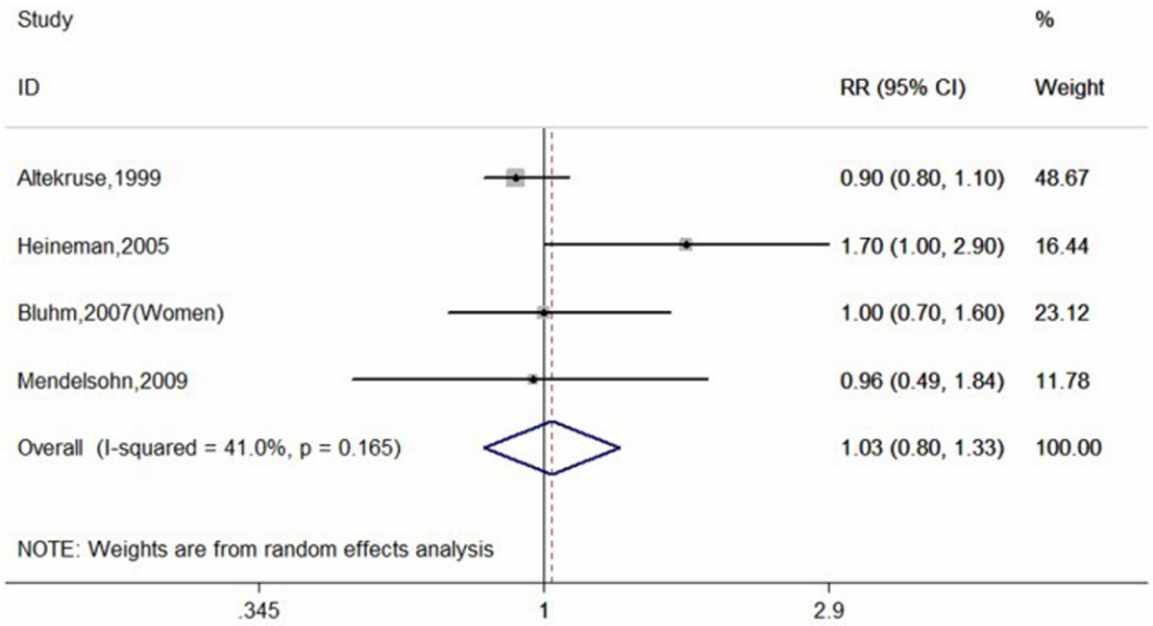

Figure 3. Forest plot of risk estimates of the association between any hair dyes use and risk of female glioma.

Results

Literature search and study characteristics

Figure 1 shows a flow diagram of literature search and selection. A total of 36 relevant studies were initially identified. After careful review, 10 studies with full text that met the inclusion criterion were assessed. Of 10, three articles investigating childhood brain tumors as subjects were excluded; two studies were reported from the same population [14, 15], and the most recent article was chosen [15]. Therefore, a final total of six studies [12, 13, 15-18] published from 1986 to 2009 were included in this meta-analysis. All of studies were published in English. Among these studies, three studies focused on women [15, 16, 18], one reported data for women and men separately [17], and two involved both women and men [12, 13]. Most of the studies concerned glioma [12, 13, 16, 17], while two reported total brain tumor or nervous system tumor [15, 18]. The additional characteristics of the selected studies are presented in **Table 1**.

Results of meta-analyses

Figure 2 shows the RRs and 95% CIs of glioma for any hair dyes users versus non users from cohort and case-control studies. Among four case-control studies, the summary RR was 1.291 (95% CI = 0.938-1.777, p for heterogeneity = 0.130, I^2 = 43.8%). Among two cohort studies, the pooled RR was 0.903 (95% CI = 0.774-1.054, p for heterogeneity = 0.853, I^2 = 0.0%). When the cohort and case-control data were combined, the cumulative risk estimate was 1.132 (95% CI = 0.887-1.446, p for heterogeneity = 0.056, I^2 = 51.5%). Excluding the two studies which reported data about all brain tumors together [15, 18], a similar result was detected (RR = 1.291, 95% CI = 0.938-1.777, p for heterogeneity = 0.130, I^2 = 43.8%). When subgroup analyses were conducted according to geographic regions, no significant correlation was observed in neither USA (RR = 1.009, 95% CI = 0.799-1.275, p for heterogeneity = 0.161, I^2 = 41.7%) nor other countries (RR = 1.450, 95% CI = 0.923-2.278, p for heterogeneity = 0.265, I^2 = 24.7%).

Figure 3 shows the RRs and 95 % CIs of female glioma for any hair dyes users versus non users from cohort and case-control studies. The pooled estimate of risk was 1.032 (95% CI = 0.801-1.329, p for heterogeneity = 0.165, I^2 = 41.0%) for all studies. Among six studies, only one study reported the association between hair dyes use and male glioma risk [17]. Bluhm and colleagues found that any hair dyes use was not associated with risk of glioma in men (OR = 0.9, 95% CI = 0.6-1.5).

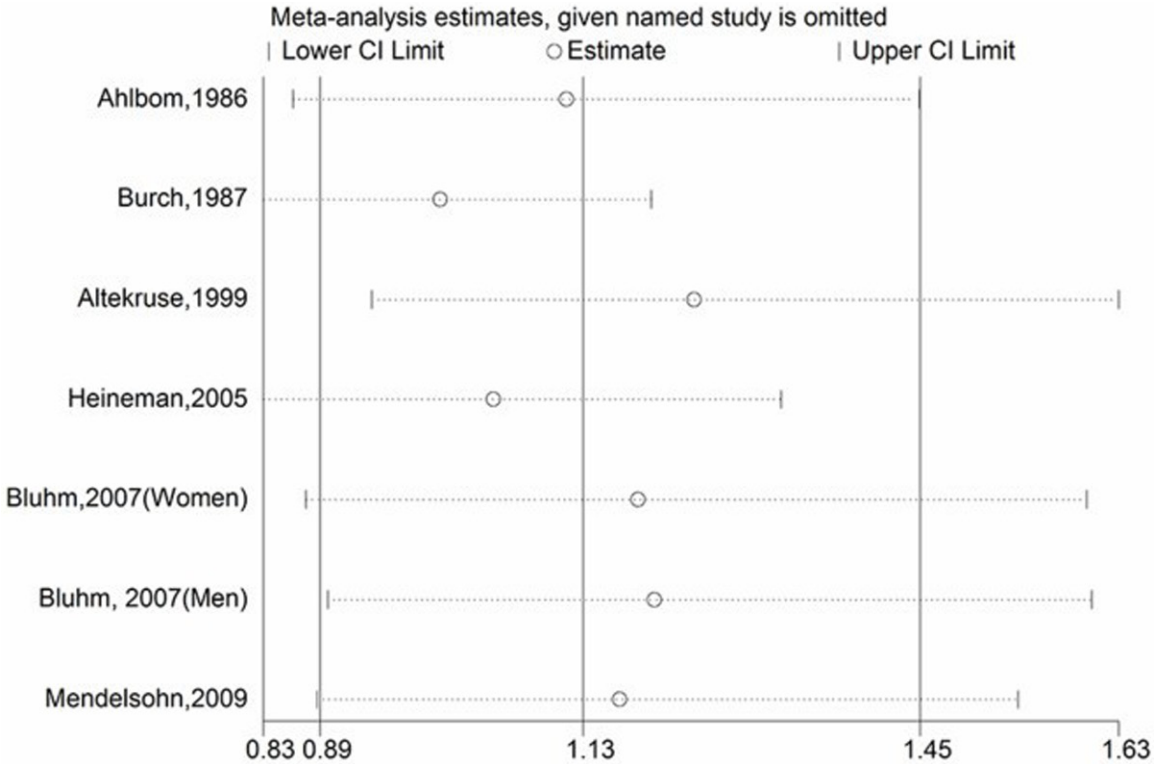

Figure 4. Sensitivity analyses through deletion of one study at a time to reflect the influence the individual study to the pooled RR for any hair dyes users versus non users.

Three studies provided results on permanent hair dye use [15-17]. The result was not presented by study design because small numbers of studies. The combined RR for cohort and case-control studies was 1.228 (95% CI = 0.810-1.862, p for heterogeneity = 0.017, I^2 = 70.5%).

Four studies provided results on duration of any hair dyes use among women. Given differences in the categorization of exposure data in the individual studies, we computed summary relative risk estimates using data for the highest exposure category of duration of any hair dye use. The pooled RRs were 0.997 (95% CI = 0.759-1.310, p for heterogeneity = 0.781, I^2 = 0.0%).

Sensitivity analysis and publication bias

In the sensitivity analysis, we excluded one single study each turn to investigate the influence of a single study on the overall risk estimate. The corresponding RRs for any hair dyes users versus non users were not significantly altered, as is shown in **Figure 4**. Result of Egger' test suggested there was little evidence of publication bias (P = 0.094).

All results were also presented in **Table 2**.

Discussion

This meta-analysis including four case-control studies and two cohort studies showed that there is no significant link between any hair dyes use and risk of glioma. These findings were consistent with most of the included studies [12, 15, 17, 18], regardless of design or type of cases (incident or fatal cases). When subjects were limited to female, the similar trend was also observed. Since only one study involved men as subjects, we failed to assess the association between hair dyes use and glioma risk among men.

With regard to type of hair dyes use, Altekruse et al [15] first reported no statistically significant association was observed between ever use of permanent hair coloring products and brain tumor (RR = 0.9, 95% CI = 0.8-1.1). Subsequently, two case-control studies provid-

Table 2. Summary relative risk estimates between glioma risk and duration of any hair dyes use

Group	Meta-analysis			
	Number of studies	Pooled RR (95% CI)	P_Q	I^2
Ever vs. Never use (any hair dyes)				
Total	6	1.132 (0.887-1.446)	0.056	51.5%
Study design				
Case-control studies	4	1.291 (0.938-1.777)	0.130	43.8%
Cohort studies	2	0.903 (0.774-1.054)	0.853	0.0%
Geographic region				
USA	3	1.009 (0.799-1.275)	0.161	41.7%
Others	3	1.450 (0.923-2.278)	0.265	24.7%
sex				
female	4	1.032 (0.801-1.329)	0.165	41.0%
male	1	0.9 (0.6-1.5)	NA	NA
Ever vs. Never use (permanent hair dyes)	3	1.228 (0.810-1.862)	0.017	70.5%
Duration of any hair dyes use				
Highest vs. Lowest	4	0.997 (0.759-1.310)	0.781	0.0%

NA, data not available.

ed more detailed analyses of type of hair dyes use [16, 17]. Heineman et al [16] found that risks were elevated only for permanent hair dyes (OR = 2.4, 95% CI = 1.3-4.5), not for gradual (OR = 1.7, 95% CI = 0.4-6.6) or non-permanent hair dyes (OR = 1.0, 95% CI = 0.5-1.9). Bluhm and colleagues found that permanent (women: OR = 1.0, 95% CI = 0.7-1.6; men: OR = 1.4, 95% CI = 0.7-2.7), semi-permanent (women: OR = 1.0, 95% CI = 0.6-1.6; men: OR = 1.0, 95% CI = 0.4-2.7), temporary (women: OR = 0.8, 95% CI = 0.5-1.5; men: OR = 1.7, 95% CI = 0.5-5.7), gradual (women: OR = 2.0, 95% CI = 0.6-6.3; men: OR = 0.6, 95% CI = 0.3-1.3), and exclusively permanent (women: OR = 1.1, 95% CI = 0.7-2.0; men: OR = 1.5, 95% CI = 0.7-3.4) hair dyes use were not associated with a higher risk of glioma among women and men [17]. Among these studies, permanent hair dyes was the major type. We combined the data and found no evidence of an association between personal use of permanent hair dye and glioma risk (RR = 1.23, 95% CI = 0.81-1.86).

Concerning about color of hair dye has been reported in two studies [16, 17]. Heineman et al [16] reported that usual brown/brunette of permanent hair dyes use was associated with an increased female glioma risk (OR = 4.4, 95% CI = 1.7-11.4), whereas usual brown/brunette of non-permanent hair dyes use was not associated with a higher risk of female glioma (OR = 0.9, 95% CI = 0.4-2.2). Bluhm et al [17] found that there was no significant association between any color of permanent hair dyes use and glioma risk. But a higher risk of glioma was observed among women who used brown permanent hair dye more than twenty years (OR = 3.8, 95 CI: 1.2-12.5) and red permanent hair dye less than twenty years (OR = 3.3, 95 CI: 1.0-10.8) [17]. There is not a straightforward explanation for this apparent discrepancy on the effects of different colors of hair dye. In our view, one possible explanation is that the results got by chance because comparisons for different colors based on small number of exposed subjects and limited number of studies. Another is that a hypothesis is that substances contained in different color hair dyes products have different effects.

Assessment of dose–response in observational studies is considered to be a major criterion for determination of the causality of an association. However, we failed to perform dose-response analysis of duration and frequency of any particular types of hair dyes use because of insufficient data in most studies and differences in the categorization of exposure data in the individual studies. However, we evaluated the highest level of duration of any hair dyes use versus the lowest exposure in this meta-analysis. The lowest exposure was defined as never users of any hair dyes. The pooled result shows that increasing duration of use was not significantly associated with glioma risk (RR = 0.997,

95% CI = 0.759-1.310, p for heterogeneity = 0.781, I^2 = 0.0%).

Some limitations of this study should be addressed as well. First, most of included studies were provided the retrospective evidence. Thus, the recall and selection bias may confounder the relationship. Second, most risk estimates were derived from multivariable models, but individual studies did not adjust for potential risk factors in a consistent way. Therefore, the combined estimation might provide less clear results. Third, all studies included in this meta-analysis were published in English. The exclusion of other language publications might induce language bias. Finally, potential publication bias might influence our findings although no evidence of publication bias was observed in the present meta-analysis.

In conclusion, our meta-analysis suggests that personal use of hair dyes is not a risk factor for glioma. More studies are needed to confirm this finding.

Disclosure of conflict of interest

No conflicts of interest were disclosed.

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