RESEARCH COMMUNICATION

Lack of Association Between GSTM1 and GSTT1 Polymorphisms and Brain Tumour Risk

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Abstract

Objective: Glutathione S-transferases (GSTs) are important enzymes that are involved in detoxification of environmental carcinogens. Molecular epidemiological studies have been conducted to investigate the association between GSTM1 and GSTT1 homozygous deletion polymorphisms and brain tumours but results have been conflicting. The aim of this study was to clarify this problem using a meta-analysis. Methods: A total of 9 records were identified by searching the PubMed and Embase databases. Fixed- and random-effects models were performed to estimate the pooled odds ratios. Results: No significant association was found between the GSTM1 and GSTT1 homozygous deletion polymorphisms and risk of brain tumours, including glioma and meningioma. Similar negative results were also observed in both population-based and hospital-based studies. Conclusion: These findings indicate that the GSTM1 and GSTT1 polymorphisms may not be related to the development of brain tumours.

Keywords: GSTM1 - GSTT1 - polymorphism - brain tumours - meta-analysis

Asian Pacific J Cancer Prev, **13**, 325-328

Introduction

Although they are rarely spread to other organs of the body, brain tumors are life-threatening because they can increase pressure in the brain, push the brain against the skull, and invade healthy brain tissue. It is estimated that 22,020 new cases and 13,140 deaths occurred in 2010 (Jemal et al., 2010). The etiology of brain tumors is poorly understood. However, growing evidence has shown that genetic and environmental characteristics play key roles in the development of brain tumors (Inskip et al., 1995; Fisher et al., 2007).

Glutathione S-transferases (GSTs) are important enzymes that are involved in detoxification of varieties of environmental carcinogens (Hayes and Pulford 1995). The soluble GSTs are divided into four main classes: α (GSTA), μ (GSTM), π (GSTP), and θ (GSTT) (Hayes and Pulford 1995). Of the four families, GSTM1 and GSTT1 polymorphisms have been studied extensively in relation to brain tumors because the homozygous deletions (null genotypes) of the two variants have no enzymatic activity. The absence of enzymatic activity may decrease cell's detoxification ability and increase individual's susceptibility to tumorigenesis (Hayes and Strange, 2000; Norppa, 2004).

Based on the biological function of GSTs in carcinogenesis, several molecular epidemiological studies have been done to investigate the association between GSTM1 and GSTT1 polymorphisms and brain tumors (Elexpuru-Camiruaga et al., 1995; Trizna et al., 1998; Kondratieva et al., 2000; Ezer et al., 2002; De Roos et al., 2003; Wrensch et al., 2004; Pinarbasi et al., 2005; Schwartzbaum et al., 2007; Custodio et al., 2010). However, the results were conflicting. Since an individual study may have lower power to detect the association between the GSTM1 and GSTT1 polymorphisms and susceptibility to brain tumors. In this study, we conducted a meta-analysis to increase the statistical power by pooling all the eligible data together.

Materials and Methods

Selection of published studies and data extraction

PubMed and Embase databases were searched for relevant reports on the association between GSTM1 and/or GSTT1 polymorphisms and brain tumor (last search: Aug 12, 2011). The following terms were used: (GST or glutathione S-transferase) polymorphism and brain tumor. The inclusion criteria were as follows: (i) observational studies investigating the association between GSTM1 and/or GSTT1 polymorphisms and risk of brain tumors; (ii) case-control studies; and (iii) articles presentation of sufficient data for computing odds ratios (ORs). All languages were considered. The exclusion criteria were (i) investigations of association between GSTM1 and/or GSTT1 polymorphisms and survival in brain tumors; (ii) study of meta-analysis.

Two investigators (Sima and You) worked independently to abstract the following data into predetermined forms: the first author's name, the year

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Table 1. Characteristics of Studies Included in This Meta-analysis

References	Year of publication	Country (region)	Year of sample collection	Types of brain tumor (n)	Controls (n)	Matching criteria	Polymorphisms evaluated
Coutinho	2010	Brasil (Rio de Janeiro)	1998-2000	Glioma (78)	347	-	GSTM1/GSTT1
De Roos	2003	USA (Maryland)	1994-1998	Glioma (422); Meningioma (172); Acoustic neuroma (79)	GSTM1: 575 GSTT1: 545	Hospital, age, race, gender and proximity of residence to hospital	GSTM1/GSTT1
Elexpuru-Camiruaga	1995	United Kingdom (Staffordshire)	-	Glioma (109); Meningioma (50)	GSTM1: 577 GSTT1: 494	-	GSTM1/GSTT1
Ezer	2002	USA (New York)	1977-2001	Glioma (141); Neuroepithelial tumor (76)	GSTM1: 1473 GSTT1: 782	-	GSTM1/GSTT1
Kondratieva	2000	Russia (Petersburg)	-	Glioma (54)	103	-	GSTM1
Pinarbasi	2005	Turkey (Sivas)	2002	Glioma (31); Meningioma (23)	153	Age and sex	GSTM1/GSTT1
Schwartzbaum	2007	Sweden (Stockholm)	2000-2004	Glioma (343); Meningioma (176)	430	Age, sex, and region	GSTM1/GSTT1
Trizna	1998	USA (Texas)	1991-1994	Glioma (90)	90	Age, race, and gender	GSTM1/GSTT1
Wrensch	2004	USA (California)	1991-2000	Glioma (458)	GSTM1: 503 GSTT1: 504	Age, race, and gender	GSTM1/GSTT1

of publication, the country (region), the year of sample collection, types of brain tumor, the number of cases and controls, matching criteria, and quality control for the genotyping techniques (Table 1).

Statistical analysis

Pooled ORs and their 95% confidence intervals (95% CIs) were calculated separately for GSTM1 and GSTT1 polymorphisms. We detected the heterogeneity among the studies using the Q-test and I 2 statistics (Higgins and Thompson 2002). If $P > 0.10$ and $I\ 2 \leq 50\%$, we chose the fixed effects model (Mantel-Haenszel) to pool data (Mantel and Haenszel 1959). In contrast, if $P \leq 0.10$ or $I\ 2 > 50\%$, we chose the random effects model (DerSimonian and Laird) to combine data (DerSimonian and Laird, 1986). Two subgroup analyses were addressed: types of brain tumors (glioma and meningioma), and source of controls (population and hospital). Publication bias was assessed using Begg's funnel plot asymmetry test (Begg and Mazumdar, 1994), and the level of statistical significance was set at 0.05. All statistical analyses were conducted using STATA statistical software, version 10.0 (STATA Corp., College Station, TX).

Results

Study Characteristics

Totally, 96 records were retrieved through searching the PubMed and Embase databases. Among them, thirty-four were excluded because of duplicate. The remaining records were reviewed, and forty-five were excluded because they were review articles or were absence of polymorphism, brain tumor, human studies and controls. We further excluded eight studies due to overlapped data (n=3), meta-analysis (n=1), no GSTM1 and/or GSTT1 polymorphism (n=2), no brain tumor (n=1) and no available data (n=1). Finally, 9 publications were included in this meta-analysis (for GSTM1 polymorphism: 2288 cases of brain tumor and 4251 controls; and for GSTT1 polymorphism: 2201 cases of brain tumor and 3345 controls) (Figure 1).

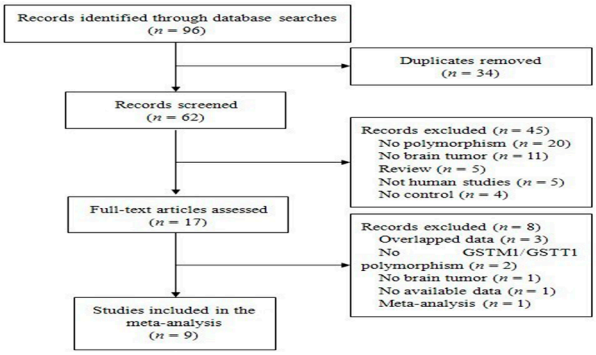

Figure 1. Flow Diagram of the Selection of Eligible Studies

The characteristics of the eligible studies are summarized in Table 1. All studies investigated the association between GSTM1 and/or GSTT1 polymorphism(s) and risk of brain tumors. For GSTM1 polymorphism, 9 studies examined the relationship in glioma, and 4 studies examined the relationship in meningioma. There were 3 population-based studies, 5 hospital-based studies, and one study without available data. For GSTT1 polymorphism, 8 studies examined the relationship in glioma, and 4 studies examined the relationship in meningioma. Three studies recruited population-based controls, and 5 studies recruited hospital-based controls. All the brain tumors were diagnosed with histopathological confirmation. All the studies reported quality control measures to avoid genotyping error, including internal control, negative control, duplicate experiments and blindness to case-control status. Five studies mentioned matching variables, and the most common matching factors were age and sex.

Meta-analysis

The results of this meta-analysis are presented in Tables 2 and 3. None of two polymorphisms exhibited a significant association with either glioma (for GSTM1: OR = 1.01; 95% CI, 0.90-1.14; and for GSTT1: OR = 1.12; 95% CI, 0.86-1.45) or meningioma (for GSTM1: OR = 1.17; 95% CI, 0.77-1.79; and for GSTT1: OR = 1.59; 95% CI, 0.91-2.78). In subgroup analyses according to source of controls, no significant association was also observed

Table 2. Meta-analysis of GSTM1 Polymorphism and the Risk of Brain Tumor

GSTM1	Number of studies	Cases/controls	Test for heterogeneity		Model for meta-analysis	Null versus present
			I^2 (%)	P heterogeneity		OR (95%CI)
Glioma	9	1697/4251	39.3	0.11	Fixed-effects model	1.01 (0.90-1.14)
Population	3	932/2406	10.5	0.33	Fixed-effects model	0.96 (0.81-1.13)
Hospital	5	711/1742	59.5	0.04	Random-effects model	1.24 (0.90-1.73)
Meningioma	4	417/1735	66.5	0.03	Random-effects model	1.17 (0.77-1.79)

Table 3. Meta-analysis of GSTT1 Polymorphism and the Risk of Brain Tumor

GSTT1	Number of studies	Cases/controls	Test for heterogeneity		Model for meta-analysis	Null versus present
			I^2 (%)	P heterogeneity		OR (95%CI)
Glioma	8	1626/3345	59.6	0.015	Random-effects model	1.12 (0.86-1.45)
Population	3	932/1716	54.5	0.11	Random-effects model	1.03 (0.74-1.43)
Hospital	5	694/1629	66.3	0.018	Random-effects model	1.19 (0.78-1.82)
Meningioma	4	405/1622	72.6	0.012	Random-effects model	1.59 (0.91-2.78)

in both population-based studies (for GSTM1: OR = 0.96; 95% CI, 0.81-1.13; and for GSTT1: OR = 1.03; 95% CI, 0.74-1.43) and hospital-based studies (for GSTM1: OR = 1.24; 95% CI, 0.90-1.73; and for GSTT1: OR = 1.19; 95% CI, 0.78-1.82).

Publication Bias

Publication bias was detected in the studies investigating the association between GSTM1 polymorphism and risk of glioma (P = 0.017). No evidence of publication bias in other studies was observed.

Discussion

In this study, we did not find any association between the GSTM1 and GSTT1 polymorphisms and risk of brain tumors, including glioma and meningioma. Similar negative results were also observed in both population-based studies and hospital-based studies. These results provide evidence to support the data reported by Coles et al. who found that GST polymorphism was not a powerful predictor of tissue-specific GST expression (Coles and Kadlubar, 2003). Taken together, we may conclude that GSTM1 and GSTT1 homozygous deletion polymorphisms may not relate to the development of brain tumors.

Some of our findings were similar to the results of a meta-analysis presented by Lai et al. in 2005 (Lai et al., 2005). In that meta-analysis, the authors searched publications up to January 2005, and found no significant association between GSTM1 and GSTT1 polymorphisms and risk of glioma. In contrast, some of our findings were in disagreement with the results reported by Lai et al. who found that the GSTT1 null genotype was significantly associated with an increased risk of meningioma (OR =1.95; 95% CI, 1.02-3.76, P = 0.046) (Lai et al., 2005). The main reason for this discrepancy may be that the statistical power is not sufficient to provide accurate effect of GSTT1 polymorphism on the risk of meningioma. Only 3 studies with 242 cases and 1251 controls were available for assessing the relationship between GSTT1 polymorphism and meningioma susceptibility in that meta-analysis (Elexpuru-Camiruaga et al., 1995; De Roos et al., 2003; Pinarbasi et al., 2005). Moreover, the significance is marginal. When an additional study was included in this meta-analysis (Schwartzbaum et al., 2007), the power was increased with much more sample sizes, and the significant difference disappeared.

When stratified according to source of controls, we failed to find that the GSTM1 and GSTT1 polymorphisms could influence the risk of brain tumors in both population-based studies and hospital-based studies. Further subgroup analyses (e.g, age, and ethnicity) were prevented due to lack of sufficient data.

Publication bias is very important in a meta-analysis. And thus we used Begg's funnel plot to assess this issue and found publication bias exhibiting in association studies between GSTM1 polymorphism and risk of glioma, indicating that there is a high risk of selective publication of reports because of unknown reasons.

Some limitations should be addressed in this meta-analysis. Currently, it is widely recognized that the interaction of both environmental and genetic factors may contribute to the development of brain tumors (Inskip et al., 1995; Fisher et al., 2007). It is an important priority for understanding the effect of the interaction of GSTM1 and GSTT1 homozygous deletion polymorphisms and environmental exposure on the individual's susceptibility to brain tumors. However, the investigation of gene-environment interactions was not available in this meta-analysis because of absence of detailed information. Additionally, the lack of enough data precludes examination of gene-gene interactions. On the other hand, the power might not be sufficient owing to the relatively small sample size included in this study, which may be responsible for the negative results of the association between the GSTM1 and GSTT1 homozygous deletion polymorphisms and risk of brain tumors.

In conclusion, the results of this meta-analysis suggest that the GSTM1 and GSTT1 polymorphisms are not associated with the susceptibility to brain tumors. Further studies with larger sample size in diverse ethnic groups are warranted to confirm these findings. Additionally, association studies evaluating the effect of gene-gene and gene-environment interactions on the risk of brain tumors would be valuable.

Acknowledgements

The author(s) declare that they have no competing interests.

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