Association between GSTM1 and GSTT1 Allelic Variants and Head and Neck Squamous Cell Cancinoma

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Abstract

Backgrounds: GSTM1 and GSTT1 are involved in the detoxification of carcinogens such as smoking by-products, and polymorphisms in these two genes with a result of loss of enzyme activity may increase risk of carcinogenesis. Although many epidemiological studies have investigated the association between GSTM1 or GSTT1 null genotype and head and neck squamous cell carcinoma (HNSCC), the results remain conflicting. To elucidate the overall association of GSTM1, GSTT1 and HNSCC, we included all available studies and performed this meta-analysis.

Methodology/Principal Findings: A dataset including 42 articles for *GSTM1*, 32 articles for *GSTT1*, and 15 articles for *GSTM1* and *GSTT1* in combination were identified by a search in PubMed. Associations beween HNSCC and polymorphisms of *GSTM1* and *GSTT1* alone and in combination were analysed by software RevMan 5.1. Stratification analysis on ethnicity and smoking status, sensitivity analysis, heterogeneity among studies and their publication bias were also tested. Association was found in overall analysis between HNSCC and *GSTM1* and *GSTT1* null genotype. Stratified by ethnicity, we found increased risks of HNSCC in carriers with *GSTM1* null genotype in Asian, *GSTT1* null genotype in South American, and dual null genotype in European and Asian. When stratified by smoking, a more significant association of *GSTM1* null genotype with HNSCC risk was observed in smokers.

Conclusions/Significance: This meta-analysis presented additional evidence of the association between *GSTM1* and *GSTT1* polymorphisms and HNSCC risk.

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Introduction

Head and neck neoplasms are the sixth leading cause of death by cancer [1]. The most common histological type is the squamous cell carcinoma, accounting for about 90% of all cases [2,3]. Being a multifactorial disease, the etiology of head and neck squamous cell carcinoma (HNSCC) is still a much debated question. Smoking of cigarettes, consumption of alcohol and genetic causes are some of the foci of former etiological studies.

Enzymes of the glutathione S-transferase (GST) family are present in eukaryotes and in prokaryotes, which are composed of many cytosolic, mitochondrial, and microsomal proteins. They catalyze various reactions and participate in the phase II biotransformation of xenobiotics. GSTs contribute to the detoxification of by-products of smoking and alcohol and other exogenous chemical carcinogens which may induce HNSCC, so they have been considered as potential candidates for HNSCC susceptibility. Classes*i* and μ of the GST superfamily have been paid lots of attention, which are encoded by *GSTT1* and *GSTM1* genes. The *GSTM1* and *GSTT1* gene have been localized to chromosome 1p13.3 and 22q11.2. Both of the genes are polymorphic and frequent homozygous deletions of the genes presenting null genotype are associated with loss of the corresponding enzyme activity. Therefore, carriers with null genotype will increase the risk of the development of HNSCC due to the decreased ability to detoxify carcinogens theoretically.

In 2003, a meta-analysis conducted by Hashibe *et al.* indicated modest associations of *GSTM1* and *GSTT1* genotypes with head and neck cancer risk [4]. However, more than twenty independent studies from various populations have further examined the relationships between these two genes and HNSCC risk, and still reported conflicting results. Some studies in HNSCC have indicated that the null genotype of *GSTM1* or *GSTT1* is a risk factor of HNSCC development [5–7]. However, such an association was not observed in some other groups [8–10]. Therefore, it is necessary to reevaluate the association of *GSTM1* or *GSTT1* null genotype with the risk of HNSCC by pooling the new published studies using meta-analysis. The present study included all eligible published case-control studies to establish a relatively comprehensive picture of the relationship between these two genes and HNSCC.

Materials and Methods

Selection criteria and identification of eligible studies

Candidate studies were identified through computer-aided literature searches in PubMed for relevant articles in English and Chinese (1995 to May 2012). To identify all articles that studied the association of GSTT1 and GSTM1 polymorphisms with HNSCC, we conducted the search using the following keywords and subject terms: 'GSTT1' or 'GSTM1', and 'squamous'. We also searched the references cited in the articles and included published works. Abstracts, case-only articles, editorials, review articles and repeated literatures were excluded. Of the articles with the overlapping data, we only included the publication with the most extensive information. The inclusion criteria in the current meta-analysis were as follows: (a) they are unrelated studies; (b) identification of squamous cell carcinoma was histologically confirmed; and (c) they have original data of genotype frequency and provided sufficient information to calculate the odds ratio (OR) or P-value.

Data extraction

Two reviewers (Zhang Y and Ni Y) independently examined the studies for inclusion in the meta-analysis and collected data on the genotype of *GSTT1* and *GSTM1*. We extracted the following

information from each study: first author, year of publication, country, ethnicity, numbers of case and control, smoking status and genotyping information. Disagreements between two reviewers were discussed and resolved with consensus. When essential information was not found in articles, we made effort to get the data from the authors (Figure 1).

Statistical analysis

The meta-analysis for *GSTM1* or *GSTT1* null genotype or dual null genotype compared HNSCC vs. controls. Odds ratio (OR) and its 95% confidence interval (CI) were assessed for each study. The Cochran's Q-statistic was used to test heterogeneity, and the heterogeneity was considered statistically significant when P < 0.1[11]. The Mantel-Haenszel method was used to calculate the OR for the included data in a fixed effects model in the absence of between-study heterogeneity. P-value<0.05 was considered statistically significant, and $0.05 \le P$ -value<0.10 was indicated suggestive. In addition, we also performed stratification analyses on ethnicity, smoking and combined analyses of *GSTM1* and *GSTT1* on HNSCC risk. The sensitivity analysis was carried out to test the stability of the pooled effect after excluding individual studies. Begg's funnel plot was used to evaluate publication bias.

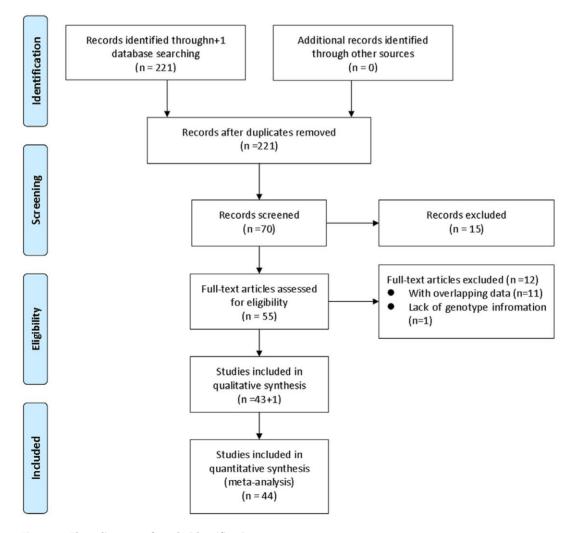


Figure 1. Flow diagram of study identification. doi:10.1371/journal.pone.0047579.g001

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

| Author (Ref) | Year | Country | Ethnicity | Case | Control | Whether has genotype distribution information | | | | | |
|-------------------------------|------|-------------|----------------|------|---------|---|-----------|------------|------------------------|--|--|
| | | | | | | GSTM1 | GSTT1 | Dual genes | Tobacco consumption | | |
| Jahnke et al. (23) | 1996 | Germany | European | 269 | 216 | Yes | Yes | No | No | | |
| Park et al. (24) | 1997 | USA | European | 133 | 133 | Yes | No | No | No | | |
| González et al. (25) | 1998 | Spain | European | 75 | 200 | Yes | No | No | No | | |
| Oude Ophuis et al. (13) | 1998 | Netherlands | European | 185 | 207 | Discarded | Discarded | Yes | No | | |
| Cheng et al. (26) | 1999 | USA | European | 162 | 315 | Yes | Yes | Yes | No | | |
| Katoh et al. (27) | 1999 | Japan | Asian | 92 | 147 | Yes | Yes | No | No | | |
| Morita et al. (28) | 1999 | Japan | Asian | 145 | 164 | Yes | No | No | No | | |
| Nazar-Stewart et al. (29) | 1999 | USA | European | 48 | 144 | Yes | No | No | Yes | | |
| Sato et al. (30) | 1999 | Japan | Asian | 142 | 142 | Yes | No | No | No | | |
| Tanimoto et al. (31) | 1999 | Japan | Asian | 100 | 100 | Yes | No | No | No | | |
| Hamel et al. (32) | 2000 | Canada | European | 90 | 90 | Yes | Yes | No | No | | |
| Olshan et al. (33) | 2000 | USA | European | 182 | 202 | Yes | Yes | No | Yes | | |
| Hahn et al. (34) | 2002 | Germany | European | 94 | 92 | Yes | No | No | No | | |
| To-Figureras et al. (35) | 2002 | Spain | European | 204 | 203 | Yes | Yes | No | No | | |
| Gronau et al. (36) | 2003 | Germany | European | 187 | 139 | Yes | Yes | Yes | No | | |
| Drummond et al. (37) | 2004 | Brazil | South American | 70 | 82 | Yes | No | No | No | | |
| Evans et al. (38) | 2004 | USA | European | 283 | 208 | Yes | Yes | No | Yes | | |
| Li et al. (39) | 2004 | China | Asian | 89 | 164 | Yes | No | No | No | | |
| Drummond et al. (40) | 2005 | Brazil | South American | 87 | 81 | No | Yes | No | No | | |
| Gajecka et al. (41) | 2005 | Poland | European | 292 | 321 | Yes | Yes | No | No | | |
| Acar et al. (42) | 2006 | Turkey | Asian | 110 | 197 | Yes | Yes | No | No | | |
| Biselli et al. (10) | 2006 | Brazil | South American | 60 | 60 | Yes | Yes | Yes | No | | |
| Gatta's et al. (43) | 2006 | Brazil | South American | 103 | 102 | Yes | Yes | Yes | No | | |
| Oude Ophuis et al. (44) | 2006 | Netherlands | European | 185 | 285 | Yes | Yes | No | No | | |
| Peters et al. (45) | 2006 | USA | European | 692 | 753 | Yes | Yes | No | Yes | | |
| Sharma et al. (46) | 2006 | India | Asian | 40 | 87 | Yes | Yes | No | Yes | | |
| Sugimura et al. (47) | 2006 | Japan | Asian | 122 | 241 | Yes | Yes | No | Yes | | |
| Anatharaman et al. (48) | 2007 | India | Asian | 451 | 727 | Yes | Yes | No | Yes | | |
| Cha et al. (49) | 2007 | Korea | Asian | 72 | 209 | Yes | No | No | Yes | | |
| Suzen et al. (8) | 2007 | Turkey | Asian | 98 | 120 | Yes | Yes | Yes | Yes | | |
| Boccia et al. (9) | 2008 | Italy | European | 210 | 245 | Yes | Yes | No | No | | |
| Buch et al. (50) | 2008 | USA | European | 196 | 414 | Yes | Yes | No | No | | |
| Harth et al. (51) | 2008 | Germany | European | 312 | 300 | Yes | Yes | No | No | | |
| Hatagima et al. (52) | 2008 | Brazil | South American | 231 | 212 | Yes | Yes | No | No | | |
| Losi-Guembarovski et al. (53) | 2008 | Brazil | South American | 91 | 81 | Yes | Yes | No | No | | |
| Amtha et al. (54) | 2009 | Indonesia | Asian | 81 | 162 | Yes | Yes | No | No | | |
| Li et al. (55) | 2009 | China | Asian | 76 | 76 | Yes | Yes | No | Yes | | |
| Chatzimichalis et al. (56) | 2010 | Greek | European | 88 | 102 | Yes | Yes | No | No | | |
| Leme et al. (57) | 2010 | Brazil | South American | 100 | 100 | Yes | Yes | Yes | No | | |
| Sam et al. (58) | 2010 | India | Asian | 408 | 220 | Yes | Yes | Yes | No | | |
| Soucek et al. (59) | 2010 | Czech | European | 122 | 179 | Yes | Yes | No | No | | |
| Lourenço et al. (6) | 2011 | Brazil | South American | 142 | 142 | Yes | Yes | No | No | | |
| Ruwali et al. (5) | 2011 | India | Asian | 500 | 500 | Yes | Yes | Yes | Yes | | |
| Shukla et al. (60) | 2012 | India | Asian | 150 | 141 | Yes | No | No | No | | |

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| atudy or Subgroup ahnke et al. 1996 | Events | Total | Events | Total | Weight | M-H Random 95% Cl | | |
|---|------------------------|-----------|-----------|--------|--------------------------|---------------------|------|---------------------|
| ahnke et al. 1996 | | 000 | | | - | M-H, Random, 95% CI | | M-H, Random, 95% Cl |
| | 151 | 269 | 112 | 216 | 2.8% | 1.19 [0.83, 1.70] | | |
| Park et al. 1997 | 68 | 133 | 68 | 133 | 2.4% | 1.00 [0.62, 1.62] | | |
| Sonzález et al. 1998 | 44 | 75 | 103 | 200 | 2.2% | 1.34 [0.78, 2.29] | | |
| Aorita et al. 1999 | 71 | 145 | 83 | 164 | 2.5% | 0.94 [0.60, 1.46] | | |
| animoto et al. 1999 | 43 | 100 | 42 | 100 | 2.1% | 1.04 [0.59, 1.83] | | |
| Catoh et al. 1999 | 54 | 92 | 68 | 147 | 2.2% | 1.65 [0.98, 2.80] | | |
| Cheng et al. 1999 | 86 | 162 | 135 | 315 | 2.7% | 1.51 [1.03, 2.21] | | |
| Sato et al. 1999 | 92 | 142 | 64 | 142 | 2.4% | 2.24 [1.39, 3.61] | | |
| lazar-Stewart et al. 1999 | 26 | 48 | 63 | 142 | 1.8% | 1.48 [0.77, 2.86] | | |
| lamel et al. 2000 | 51 | 90 | 52 | 90 | 2.0% | 0.96 [0.53, 1.72] | 2000 | |
| Dishan et al. 2000 | 76 | 176 | 88 | 195 | 2.6% | 0.92 [0.61, 1.39] | 2000 | - |
| lahn et al. 2002 | 56 | 94 | 49 | 92 | 2.1% | 1.29 [0.72, 2.31] | 2002 | |
| o-Figureras et al. 2002 | 96 | 204 | 100 | 203 | 2.7% | 0.92 [0.62, 1.35] | 2002 | - |
| Gronau et al. 2003 | 80 | 187 | 68 | 139 | 2.5% | 0.78 [0.50, 1.21] | 2003 | |
| vans et al. 2004 | 136 | 282 | 102 | 208 | 2.8% | 0.97 [0.68, 1.39] | 2004 | + |
| rummond et al. 2004 | 46 | 70 | 40 | 82 | 1.8% | 2.01 [1.04, 3.88] | 2004 | |
| i et al. 2004 | 50 | 89 | 69 | 164 | 2.2% | 1.77 [1.05, 2.97] | 2004 | |
| Sajecka et al. 2005 | 140 | 292 | 164 | 321 | 2.9% | 0.88 [0.64, 1.21] | 2005 | |
| car et al. 2006 | 57 | 110 | 74 | 197 | 2.4% | 1.79 [1.11, 2.87] | 2006 | |
| Sharma et al. 2006 | 21 | 40 | 29 | 87 | 1.6% | 2.21 [1.03, 4.75] | 2006 | |
| Satta' s et al. 2006 | 59 | 103 | 39 | 102 | 2.1% | 2.17 [1.24, 3.79] | 2006 | |
| Peters et al. 2006 | 403 | 692 | 404 | 753 | 3.3% | 1.20 [0.98, 1.48] | 2006 | - |
| Biselli et al. 2006 | 25 | 60 | 29 | 60 | 1.7% | 0.76 [0.37, 1.57] | 2006 | |
| Sugimura et al. 2006 | 59 | 122 | 126 | 241 | 2.5% | 0.85 [0.55, 1.32] | 2006 | |
| Oude Ophuis et al. 2006 | 94 | 185 | 163 | 285 | 2.7% | 0.77 [0.53, 1.12] | 2006 | - |
| cha et al. 2007 | 37 | 72 | 123 | 209 | 2.2% | 0.74 [0.43, 1.27] | 2007 | |
| natharaman et al. 2007 | 198 | 451 | 269 | 727 | 3.2% | 1.33 [1.05, 1.69] | | - |
| Suzen et al. 2007 | 67 | 98 | 57 | 120 | 2.1% | 2.39 [1.37, 4.17] | 2007 | |
| latagima et al. 2008 | 95 | 231 | 93 | 212 | 2.7% | 0.89 [0.61, 1.30] | | - |
| larth et al. 2008 | 166 | 612 | 145 | 300 | 3.0% | 0.40 [0.30, 0.53] | 2008 | + |
| osi-Guembaro et al. 2008 | 36 | 91 | 42 | 81 | 2.0% | 0.61 [0.33, 1.11] | 2008 | |
| Boccia et al. 2008 | 112 | 210 | 128 | 245 | 2.7% | 1.04 [0.72, 1.51] | | + |
| Buch et al. 2008 | 126 | 196 | 276 | 414 | 2.8% | 0.90 [0.63, 1.29] | | - |
| i et al. 2009 | 45 | 76 | 32 | 76 | 1.9% | 2.00 [1.05, 3.81] | | |
| mtha et al. 2009 | 49 | 81 | 90 | 162 | 2.2% | 1.23 [0.71, 2.11] | | |
| eme et al. 2010 | 66 | 100 | 75 | 100 | 2.0% | 0.65 [0.35, 1.19] | | + |
| Soucek et al. 2010 | 64 | 116 | 70 | 122 | 2.3% | 0.91 [0.55, 1.53] | | + |
| Chatzimichal et al. 2010 | 74 | 88 | 88 | 102 | 1.5% | 0.84 [0.38, 1.88] | | |
| Sam et al. 2010 | 109 | 408 | 48 | 220 | 2.7% | 1.31 [0.89, 1.93] | | + |
| Ruwali et al. 2011 | 236 | 500 | 160 | 500 | 3.1% | 1.90 [1.47, 2.46] | | - |
| ourenço et al. 2011 | 58 | 142 | 66 | 142 | 2.4% | 0.80 [0.50, 1.27] | | -+ |
| Shukla et al. 2012 | 51 | 150 | 27 | 141 | 2.2% | 2.18 [1.27, 3.73] | | |
| otal (95% CI) | | 7584 | | 8651 | 100.0% | 1.14 [1.00, 1.29] | | • |
| otal events | 3673 | | 4123 | | | | | |
| leterogeneity: Tau ² = 0.12; C | Chi ² = 147 | .35, df = | = 41 (P < | 0.0000 | 1); l ² = 72% | 6 | | 0.01 0.1 1 10 100 |

Figure 2. Forest plot of GSTM1 associated with HNSCC under random-effects model. Each study is shown by point estimate of OR and 95% CI by a horizontal line. The diamond shows the overall risk and the line represent the 95% CI for each meta-analysis. Events: null genotype. doi:10.1371/journal.pone.0047579.g002

| | GSTM1 | | | GSTT1 | | | GSTM1+GSTT1 | | | |
|---------------------------|-----------|--------------|-----------|-----------|-----------|-----------|-------------|-----------|-----------|--|
| | European | Asian | South Am | European | Asian | South Am | European | Asian | South Am | |
| Cases (n/N ^a) | 2049/4111 | 1239/2676 | 385/797 | 766/3458 | 497/1983 | 280/814 | 83/534 | 200/1769 | 48/354 | |
| Controls (n/N) | 2378/4475 | 1361/3397 | 384/779 | 849/3884 | 586/2476 | 205/778 | 57/661 | 185/2088 | 48/343 | |
| OR ^b | 0.96 | 1.48 | 1.05 | 1.21 | 1.32 | 1.63 | 2.01 | 1.56 | 0.96 | |
| 95% Cl ^c | 0.82-1.13 | 1.24–1.75 | 0.71-1.57 | 0.87–1.69 | 0.93–1.88 | 1.03–2.58 | 1.15–3.53 | 1.05-2.33 | 0.62-1.48 | |
| P ^d | 0.64 | < 0.00001*** | 0.80 | 0.26 | 0.12 | 0.04* | 0.01* | 0.03* | 0.85 | |

Abbreviations: ^a, number of carriers with null genotype/ total number; ^b, odds ratio; ^c, confidence interval; ^d, value for heterogeneity; OR, odds ratio; 95% CI, 95% confidence interval. **P <0.01; * 0.01≤P<0.05

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| A | Cases | | Contro | | | Odds Ratio | | Odds Ratio |
|---|--|--|---|--|--|---|--|--|
| Study or Subgroup | | | Events | 0.000000 | | M-H. Random, 95% CI | 1000 | M-H. Random, 95% Cl |
| Jahnke et al. 1996 | 56 | 269 | 27 | 215 | 3.2% | 1.83 [1.11, 3.02] | | |
| Katoh et al. 1999 | 44 | 92 | 75 | 147 | 3.2% | 0.88 [0.52, 1.48] | | |
| Cheng et al. 1999 | 53 | 162 | 55 | 315 | 3.4% | 2.30 [1.48, 3.56] | | |
| Hamel et al. 2000 | 70 | 90 | 9 | 90 | 2.4% | 31.50 [13.47, 73.64] | | |
| Olshan et al. 2000 | 32 | 176 | 26 | 195 | 3.1% | 1.44 [0.82, 2.54] | 2000 | |
| To-Figueras et al. 2002 | 35 | 204 | 48 | 203 | 3.3% | 0.67 [0.41, 1.09] | 2002 | |
| Gronau et al. 2003 | 30 | 187 | 21 | 139 | 3.0% | 1.07 [0.59, 1.97] | 2003 | |
| Evans et al. 2004 | 54 | 283 | 58 | 203 | 3.4% | 0.59 [0.39, 0.90] | 2004 | |
| Gajecka et al. 2005 | 54 | 289 | 61 | 316 | 3.4% | 0.96 [0.64, 1.44] | 2005 | + |
| Drummond et al. 2005 | 73 | 87 | 34 | 81 | 2.7% | 7.21 [3.50, 14.84] | 2005 | |
| Sugimura et al. 2006 | 46 | 122 | 105 | 241 | 3.4% | 0.78 [0.50, 1.22] | 2006 | |
| Biselli et al. 2006 | 20 | 60 | 14 | 60 | 2.5% | 1.64 [0.74, 3.67] | 2006 | |
| Peters et al. 2006 | 122 | 692 | 162 | 753 | 3.7% | 0.78 [0.60, 1.01] | | |
| Gatta' s et al. 2006 | 25 | 103 | 18 | 102 | 2.8% | 1.50 [0.76, 2.95] | | + |
| Sharma et al. 2006 | 17 | 40 | 13 | 87 | 2.4% | 4.21 [1.78, 9.95] | | |
| Acar et al. 2006 | 33 | 110 | 31 | 197 | 3.1% | | 2006 | |
| Oude Ophuis et al. 2006 | 36 | 185 | 94 | 285 | 3.4% | 0.49 [0.32, 0.76] | | |
| Anantharaman et al. 2007 | 45 | 456 | 114 | 726 | 3.5% | 0.59 [0.41, 0.85] | | |
| Suzen et al. 2007 | 19 | 98 | 23 | 120 | | | | |
| | | | | | 2.8% | 1.01 [0.52, 1.99] | | |
| Buch et al. 2008 | 67 | 195 | 122 | 414 | 3.5% | 1.25 [0.87, 1.80] | | |
| Losi-Guembaro et al. 2008 | 30 | 91 | 23 | 81 | 2.9% | 1.24 [0.65, 2.38] | | |
| Hatagima et al. 2008 | 49 | 231 | 48 | 212 | 3.3% | 0.92 [0.59, 1.44] | | 1 |
| Harth et al. 2008 | 64 | 312 | 61 | 300 | 3.5% | 1.01 [0.68, 1.50] | | |
| Boccia et al. 2008 | 48 | 210 | 58 | 245 | 3.4% | 0.96 [0.62, 1.48] | | |
| Amtha et al. 2009 | 37 | 81 | 67 | 162 | 3.1% | 1.19 [0.70, 2.04] | | |
| Li et al. 2009 | 44 | 76 | 39 | 76 | 2.9% | 1.30 [0.69, 2.47] | | |
| Chatzimichal et al. 2010 | 21 | 88 | 31 | 102 | 2.9% | 0.72 [0.38, 1.37] | 2010 | |
| Sam et al. 2010 | 77 | 408 | 16 | 220 | 3.1% | 2.97 [1.68, 5.22] | 2010 | · |
| Leme et al. 2010 | 47 | 100 | 41 | 100 | 3.1% | 1.28 [0.73, 2.23] | 2010 | |
| Soucek et al. 2010 | 24 | 116 | 16 | 109 | 2.8% | 1.52 [0.76, 3.04] | 2010 | |
| Ruwali et al.2011 | 135 | 500 | 103 | 500 | 3.7% | 1.43 [1.06, 1.91] | | |
| Lourenço et al. 2011 | 36 | 142 | 27 | 142 | 3.1% | 1.45 [0.82, 2.54] | | + |
| | | | | | 0/0 | into fotori, rio ij | 2011 | |
| Total (95% CI) | | 6255 | | 7138 | 100.0% | 1.32 [1.07, 1.64] | | • |
| | | | | | | | | 0.000 |
| | 1543 | | 1640 | | | | | |
| Total events | 1543 | | 1640 | | 1): 12 - 92 | 0/ | | |
| Total events Heterogeneity: Tau ² = 0.31; 0 | Chi ² = 186. | 20, df = | | | 1); l² = 83 | % | | 1 1 10 10 0.01 0.1 1 10 10 |
| Total events Heterogeneity: $Tau^2 = 0.31$; 0 Test for overall effect: $Z = 2.5$ | Chi ² = 186. | 20, df = | | | 1); l² = 83 | % | | |
| Total events Heterogeneity: Tau ² = 0.31; 0 Test for overall effect: Z = 2.5 | Chi² = 186. 54 (P = 0.0 | 20, df = 1) | = 31 (P < | 0.0000 | 1); l² = 83 | | | GSTT1 null in cases GSTT1 null in control |
| Total events Heterogeneity: Tau ² = 0.31; 0 Test for overall effect: Z = 2.5 B | Chi ² = 186. 54 (P = 0.0 Case: | 20, df = 1) s | = 31 (P < Contro | 0.0000 ols | | Odds Ratio | Year | GSTT1 null in cases GSTT1 null in contro Odds Ratio |
| Total events Heterogeneity: Tau ² = 0.31; (Test for overall effect: Z = 2.5 B Study or Subgroup | Chi ² = 186. 54 (P = 0.0 Case: Events | 20, df = 1) s Total | = 31 (P < Contro Events | 0.0000 ols Total | Weight | Odds Ratio M-H, Random, 95% C | | GSTT1 null in cases GSTT1 null in control |
| Total events Heterogeneity: Tau ² = 0.31; (Test for overall effect: Z = 2.5 B Study or Subgroup Jahnke et al. 1996 | Chi ² = 186. 54 (P = 0.0 Case: Events 56 | 20, df = 1) s <u>Total</u> 269 | = 31 (P < Contro Events 27 | 0.0000 ols <u>Total</u> 215 | Weight 3.3% | Odds Ratio <u>M-H, Random, 95% C</u> 1.83 [1.11, 3.02] | 1996 | GSTT1 null in cases GSTT1 null in contro Odds Ratio |
| Total events Heterogeneity: Tau ² = 0.31; G Test for overall effect: Z = 2.5 B Study or Subgroup Jahnke et al. 1996 Cheng et al. 1999 | Chi ² = 186. 54 (P = 0.0 Case: Events 56 53 | 20, df = 1) s <u>Total</u> 269 162 | = 31 (P < Contro Events 27 55 | 0.0000 ols <u>Total</u> 215 315 | Weight 3.3% 3.5% | Odds Ratio <u>M-H, Random, 95% C</u> 1.83 [1.11, 3.02] 2.30 [1.48, 3.56] | 1996 1999 | GSTT1 null in cases GSTT1 null in contro Odds Ratio |
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| Total events Heterogeneity: Tau ² = 0.31; G Test for overall effect: Z = 2.5 3 Study or Subgroup Jahnke et al. 1996 Cheng et al. 1999 Katoh et al. 1999 Katoh et al. 1999 Olshan et al. 2000 Hamel et al. 2000 To-Figueras et al. 2002 Gronau et al. 2003 Evans et al. 2004 Gajecka et al. 2005 Drummond et al. 2005 Sharma et al. 2006 Sharma et al. 2006 Sharma et al. 2006 Biselli et al. 2006 | Chi ² = 186. 54 (P = 0.0 Case: <u>Events</u> 56 53 44 32 70 35 30 35 30 54 54 54 73 25 17 46 620 36 | 20, df = 11) s Total 162 92 176 90 204 187 283 289 87 103 40 122 60 185 | = 31 (P < Contro Events 27 55 75 26 9 48 21 58 61 34 18 13 105 14 94 | 0.0000 Total 215 315 147 195 90 203 316 81 102 87 241 60 285 | Weight 3.3% 3.5% 3.3% 3.1% 0.0% 3.4% 3.0% 3.6% 2.6% 2.7% 2.2% 3.5% | Odds Ratio M-H, Random, 95% CJ 1.83 [1.11, 3.02] 2.30 [1.48, 3.56] 0.88 [0.52, 1.48] 1.44 [0.82, 2.54] 31.50 [13.47, 73.64] 0.67 [0.41, 1.09] 1.07 [0.59, 1.97] 0.59 [0.39, 0.90] 0.96 [0.64, 1.44] 7.21 [3.50, 14.84] 1.50 [0.76, 2.95] 4.21 [1.78, 9.95] 0.78 [0.50, 1.22] 1.64 [0.74, 3.67] 0.49 [0.32, 0.76] | 1996 1999 1999 2000 2002 2003 2004 2005 2006 2006 2006 2006 2006 2006 | GSTT1 null in cases GSTT1 null in contro Odds Ratio |
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Figure 3. Forest plot of *GSTT1* associated with HNSCC under random-effects model. A: Overall analysis. B: Sensitivity analysis with exclusion of the study by Hamel et al. 2000. The diamond shows the overall risk and the line represent the 95% CI for each meta-analysis. Events: null genotype. doi:10.1371/journal.pone.0047579.g003

All above statistical analysis was carried out using the software packages Review Manager (RevMan) 5.1.

Results

Eligible studies and meta-analysis databases

We identified 221 articles through the initial computerized search of published work. After reading titles, abstracts, 55 articles were retained. For the analysis of GSTM1 or GSTT1, after discarding 11 articles [7,12–21] due to the overlapping data and 1 article [22] due to lack of essential genotype information, 44 casecontrol studies [5,6,8-10,23-60] finally met our criteria for inclusion. Among them, 42 studies described the association between GSTM1 null genotype and HNSCC, and 32 between GSTT1 null genotype and HNSCC. For the association between dual null genotype and HNSCC, 1 discarded article [13] containing the distribution information of dual null genotype was reincorporated, and 15 studies were included (Table 1). For stratified the analyses by smoking, eight studies [5,8,29,33,45,47,48,55] for *GSTM1*, and seven studies [5,33,38,45–48] for GSTT1 were included.

Heterogeneity result

Cochran's Q tests indicated heterogeneity exist in different studies in the analysis except studies of dual genes in South American (P=0.51, $I^2=0\%$) and *GSTM1* in non-smokers (P=0.65, $I^2=0\%$). The random or fixed effect model was selected for comparisons with or without heterogeneity, respectively.

Meta-analysis results

A total of 7584 HNSCC cases and 8576 controls for *GSTM1*, 6255 cases and 7138 controls for *GSTT1*, 2657 cases and 3092 controls for dual genes were investigated.

For *GSTM1* polymorphism, the overall meta-analysis showed a suggestively increased risk in null genotype as compared to wild

genotype (OR = 1.145, 95% CI: 1.00–1.29, P=0.05) (Figure 2). In sensitivity analysis by temporarily excluding individual studies, no single study substantially affected the pooled OR, indicating that the results of these meta-analyses are stable. Analysis after stratification by ethnicity indicated *GSTM1* null genotype tended to be associated with HNSCC in Asian (OR = 1.48, 95% CI: 1.24–1.75, P<0.01), while no significant association was found in European or South American (Table 2).

For *GSTT1* polymorphism, null genotype was associated with an increased risk of HNSCC (OR = 1.32, 95% CI: 1.07–1.64, P=0.01) (Figure 3A). Sensitivity analysis showed that the association still exist even with exclusion of the study of Hamel et al. which was obviously deviating from others (OR = 1.21, 95% CI: 1.01–1.45, P=0.04) [32] (Figure 3B). Analysis stratified by ethnicity indicated that *GSTT1* null genotype increased the HNSCC risk in South American (OR = 1.63, 95% CI: 1.03– 2.58, P=0.04) (Table 2).

Combined analysis of *GSTM1* and *GSTT1* on HNSCC risk showed that OR of individuals with dual null genotype was elevated (OR = 1.48, 95% CI: 1.12–1.96, P=0.006) compared to *GSTM1* or *GSTT1* individual null genotype (Figure 4). After stratification for ethnicity, we observed a significant association for HNSCC in European (OR = 2.01, 95% CI: 1.15–3.53, P=0.01) and Asian (OR = 1.56, 95% CI: 1.05–2.33, P=0.03) populations among *GSTM1* and *GSTT1* dual null individuals (Table 2). The exclusion of individual studies did not change these results qualitatively.

We further performed stratification analysis by smoking status. As shown in Table 3, significant association of *GSTM1* deletion with risk of HNSCC was observed in smoking group (OR = 1.51, 95% CI: 1.05–2.17, P=0.03) but not in non-smoking group (OR = 1.14, 95% CI: 0.90–1.43, P=0.28). However, we did not found any significant associations for *GSTT1* in either smokers (OR = 1.01, 95% CI: 0.64–1.60, P=0.96) or non-smokers

| | Case | S | Contro | ols | | Odds Ratio | | | Odds Ratio | D | |
|---|-------------------------|----------|-----------|---------|----------|--------------------|------|-----------|----------------|----------------------------|----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% C | Year | N | I-H, Random, 9 | 95% CI | _ |
| Oude Ophuis et al. 1998 | 24 | 185 | 23 | 207 | 8.2% | 1.19 [0.65, 2.19] | 1998 | | | | |
| Cheng et al. 1999 | 32 | 162 | 25 | 315 | 8.7% | 2.86 [1.63, 5.01] | 1999 | | _ | | |
| Gronau et al. 2003 | 27 | 187 | 9 | 139 | 6.5% | 2.44 [1.11, 5.37] | 2003 | | | _ | |
| Gatta's et al. 2006 | 15 | 103 | 10 | 102 | 6.0% | 1.57 [0.67, 3.68] | 2006 | | | - | |
| Biselli et al. 2006 | 6 | 60 | 5 | 60 | 3.7% | 1.22 [0.35, 4.24] | 2006 | | | _ | |
| Acar et al. 2006 | 18 | 110 | 11 | 197 | 6.5% | 3.31 [1.50, 7.29] | 2006 | | | | |
| Sharma et al. 2006 | 6 | 40 | 5 | 87 | 3.6% | 2.89 [0.83, 10.13] | 2006 | | | | |
| Suzen et al. 2007 | 13 | 98 | 11 | 120 | 6.0% | 1.52 [0.65, 3.55] | 2007 | | | - | |
| Anantharaman et al. 2007 | 14 | 456 | 39 | 726 | 8.0% | 0.56 [0.30, 1.04] | 2007 | | | | |
| Losi-Guembaro et al. 2008 | 13 | 91 | 14 | 81 | 6.2% | 0.80 [0.35, 1.82] | 2008 | | | | |
| Amtha et al. 2009 | 22 | 81 | 36 | 162 | 8.1% | 1.31 [0.71, 2.41] | 2009 | | | | |
| Li et al. 2009 | 26 | 76 | 18 | 76 | 7.2% | 1.68 [0.82, 3.41] | 2009 | | + | - | |
| Sam et al. 2010 | 21 | 408 | 3 | 220 | 3.8% | 3.93 [1.16, 13.31] | 2010 | | | | |
| Leme et al. 2010 | 14 | 100 | 19 | 100 | 6.8% | 0.69 [0.33, 1.48] | 2010 | | | | |
| Ruwali et al. 2011 | 80 | 500 | 62 | 500 | 10.9% | 1.35 [0.94, 1.92] | 2011 | | - | | |
| Total (95% CI) | | 2657 | | 3092 | 100.0% | 1.48 [1.12, 1.96] | | | • | | |
| Total events | 331 | | 290 | | | | | | | | |
| Heterogeneity: Tau ² = 0.15; | Chi ² = 30.8 | 33, df = | 14(P = 0) | 0.006); | l² = 55% | | | | | 10 11 | H |
| Test for overall effect: Z = 2. | 76 (P = 0.0 | 006) | | | | | | 0.01 0. | | 10 10 I null in control | 00 |
| | | | | | | | | Dual null | in cases Dua | null in control | 3 |

Figure 4. Forest plot of *GSTM1* and *GSTT1* associated with HNSCC under random-effects models. The diamond shows the overall risk and the line represent the 95% CI for each meta-analysis. Events: null genotype. doi:10.1371/journal.pone.0047579.g004

Table 3. Genotype distribution of GSTM1 and GSTT1 in different smoking status.

| | GSTM1 | | GSTT1 | | | | |
|---------------------------|------------|-----------|------------|----------|--|--|--|
| | Non-smoker | Smoker | Non-smoker | Smoker | | | |
| Cases (n/N ^a) | 255/455 | 862/1638 | 94/462 | 347/1671 | | | |
| Controls (n/N) | 473/1031 | 658/1519 | 222/981 | 325/1527 | | | |
| OR ^b | 1.14 | 1.51 | 1.13 | 1.01 | | | |
| 95% Cl ^c | 0.9–1.43 | 1.05-2.17 | 0.68–1.86 | 0.64–1.6 | | | |
| P ^d | 0.28 | 0.03* | 0.64 | 0.96 | | | |

Abbreviations: ^a, number of carriers with null genotype/total number; ^b, odds ratio; ^c, confidence interval; ^d, value for heterogeneity; OR, odds ratio; 95% CI, 95% confidence interval

*0.01≤P<0.05

doi:10.1371/journal.pone.0047579.t003

(OR = 1.13, 95% CI: 0.68-1.86, P = 0.64) (Table 3), which may be due to the limited number of study with smoking information.

Publication bias

Funnel plots were performed to assess the publication bias, and these shapes did not suggest any obvious evidence of asymmetry in the analyses of *GSTM1*, gene-gene interaction, and *GSTT1* analysis stratified by smoking status. When one study [32] for *GSTT1* analysis and two studies [46,49] for *GSTM1* analysis stratified by smoking status were omitted, funnel plots illustrated symmetric shape.

Discussion

Genetic factors play an important role in the etiology of tumors. For HNSCC, genes encoding xenobiotic-metabolizing enzymes (XMEs) are some of the most likely candidates that could affect individual's susceptibility to the disease, due to their involvement of the metabolic activation and detoxification of the environmental carcinogens [61]. Conjugation is one of the most common pathways of xenobiotic metabolism and is considered phase II metabolism which is catalyzed by multiple enzyme superfamilies including Glutathione S-transferases (GSTs). GSTs mediate the reactions of glutathione with electrophiles, resulting in the elimination of potentially carcinogenic chemicals [62]. GSTM1 and GSTT1 genes belonging to GSTs have been studied extensively due to their important detoxification function and high-frequency polymorphisms. GSTM1 and GSTT1 homozygous deletions (null genotype) may lead to deficient enzyme activity [63]. In the present study, the overall frequency of GSTM1 and GSTT1 null genotype in controls were 47.65% and 23.77% respectively in accordance with other studies [64-67]. After stratification for ethnicity, the frequency of GSTM1 and GSTT1 null genotype in controls in European, Asian and South American were 53.14%, 40.06%, 49.29% and 21.86%, 23.67%, 26.34% respectively, which indicated ethnic differences.

The importance of *GSTM1* and *GSTT1* polymorphisms effects on HNSCC has been a concern in recent years, but the data of existing studies are contradictory. An increase in the risk of HNSCCC was observed in cases with null genotypes of *GSTM1* or *GSTT1* in some studies [5–8]. However the risk was not found in other studies. For example, Boccia [9] and Biselli [10] did not find the association between *GSTM1* or *GSTT1* and HNSCC. Although the confused effect of these polymorphisms may be a result of various reasons such as demographic features of subjects and different life styles, comparatively small sample size in individual study might lead to lower statistical power and bias. The present meta-analyses of 42 studies including 7584 cases and 8651 controls for analysis of *GSTM1*, 32 studies including 6255 cases and 7138 controls for analysis of *GSTT1*, and 15 studies including 2657 cases and 3092 controls provide more comprehensive information on the relationships between two genes and HNSCC.

This meta-analysis showed that both *GSTM1* and *GSTT1* null genotype confers susceptibility to HNSCC in the overall analysis. *GSTM1* can deals with large hydrophobic electrophiles including polycyclic aromatic hydrocarbons derived epoxides (PAH) [68,69], while *GSTT1* targets a more restricted kind of compounds, like monohalomethane and ethylene oxide [70]. Different GST isoforms exhibit overlapping substrate specificity, combinations of *GSTM1* and *GSTT1* null genotype may theoretically confer a higher risk to HNSCC. Comparing to homozygous deletion of *GSTM1* and *GSTT1* alone, deletion of two genes in combination significantly increases the risk of HNSCC as showed in our combined analysis, indicating a synergenic role of *GSTT1* and *GSTT1* in *GSTT1* in *GSTT1* in *GSTT1* in *GSTT1* in *GSTT1* and *GSTT1*

Analyses after stratification by ethnicity revealed ethnicityspecific associations between two genes and HNSCC. Our findings indicate that *GSTM1* may be an important factor in Asians in the development of HNSCC, which is similar to the results reported by Hashibe et al. [4]. However, *GSTT1* but not *GSTM1* may be important in South Americans, while *GSTM1* and *GSTT1* in combination play a vital role in Europeans and Asians. This result may be attributed to the different habits of smoking, alcohol consumption, intake of food and different genetic backgrounds in different ethnic groups.

Both GSTT1 and GSTM1 can prevent the accumulation of tobacco smoke carcinogens, and compared with non-smokers, mutations of these two genes theoretically increase the risk of HNSCC in smokers. To investigate potential gene-environment interaction, we stratified the data by smoking status. A significant association was observed in smokers with GSTM1, whereas no difference was observed between smokers and non-smokers for GSTT1. Previous studies showed that GSTT1 and GSTM1 are involved in the detoxification of carcinogens such as smoking byproducts, and polymorphisms in these two genes with a result of loss of enzyme activity may increase risk of carcinogenesis and have different role in detoxification. [68-70]. Although we found higher risk of GSTM1 null genotype in smokers (OR = 1.51) than non-smokers (OR = 1.14), further individual large study are required to evaluate the interaction of GSTM1 and smoking on HNSCC risk.

Although our result of this meta-analysis is constructive, its limitations and some potential bias should be addressed. First, despite that a well-designed search strategy was used to identify eligible studies, it was possible that some relevant studies were not included. This study only focused on full-text papers published in English and Chinese in PubMed, so some eligible studies in other languages or in other databases might be missed. Second, adjustments over age, gender and other environmental factors such as alcohol drinking might help better detect the association between GSTM1, GSTT1 and HNSCC. If available detailed individual data are enough for an adjusted estimate in the future, a more precise analysis should be conducted. Third, ethnicity was determined roughly by subject's country due to inadequate available data, and this classification can help us have a regional concept of these genes functions. Fourth, the controls in the included studies were recruited in different ways and not uniformly defined, which may have distorted the meta-analysis. Finally,

because all the studies were designed with retrospective studies, we cannot clearly determine the causal relationship between the risk factor and HNSCC. Given the limitations and biases above, the conclusions or interpretations made from the results of this metaanalysis should be explained with caution.

Conclusions

The results of this meta-analysis suggest that *GSTM1* and *GSTT1* null genotypes may be associated with an increased risk of HNSCC. Further large well-designed studies are warranted to confirm these findings.

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Supporting Information

Prisma Checklist S1

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Author Contributions

Conceived and designed the experiments: JM LW. Analyzed the data: YZ YN HZ. Wrote the paper: JM YP.

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