Association Between \textit{GSTM1} Null Genotype and Coronary Artery Disease Risk: A Meta-Analysis

ABCDEF 1 Mei Yang
ABCDEF 2 Jing Zhao
ABCD 1 Lin Xing
ABCD 1 Li Shi

Corresponding Author: Mei Yang e-mail: wanywn163@163.com
Source of support: Self financing

Background: We conducted a meta-analysis to assess the association between polymorphisms of \textit{GSTM1} null genotype and coronary artery disease (CAD) risk.

Material/Methods: Published literature from PubMed, EMBASE, and China National Knowledge Infrastructure (CNKI) were retrieved before March 2014. All studies reporting adjusted odds ratios (ORs) and 95\% confidence intervals (CIs) of CAD risk were included.

Results: A total of 13 case-control studies, including 5453 cases and 5068 controls, were collected. There was a significant association between \textit{GSTM1} null genotype and CAD risk (adjusted OR=1.26; 95\% CI, 1.11–1.43; $I^2=3\%$). When stratified by ethnicity, a significantly elevated risk was observed in whites. In the subgroup analysis according to disease type, a significantly increased myocardial infarction (MI) risk was observed. Subgroup analysis of smoking status showed an increased CAD risk in smokers.

Conclusions: Our results indicate that \textit{GSTM1} null genotype is associated with an increased CAD risk.

MeSH Keywords: Coronary Artery Disease \• Glutathione Transferase \• Meta-Analysis as Topic \• Polymorphism, Genetic

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/890876

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License
Background

Coronary artery disease (CAD) is the leading health problem worldwide and is the leading cause of mortality in the United States. The role of DNA oxidative stress in the pathogenesis of atherosclerosis and its association with increased production of reactive oxygen species has been well established [1]. The mutagenic activities of cigarette smoke chemicals can cause DNA adducts in target tissues and oxidative modification and progression of atherosclerotic lesions. The glutathione S-transferases (GSTs) are a gene superfamily of phase II metabolic enzymes that detoxify free radicals, particularly in tobacco smoke [2]. GSTM1 has been mapped to the GST mu gene cluster on chromosome 1p13.3. One variant in GSTM1 have been identified – a deletion. This inactive form of GSTM1 (null genotype) causes lower detoxification, which may be a risk factor for CAD. The relationship between GSTM1 null genotype and risk of CAD has been studied for more than 10 years. Several studies found GSTM1 null genotype to be a risk factor in CAD, but other studies showed no association between this polymorphism and risk of CAD. These studies reached inconsistent conclusions [3–15], probably due to the relatively small sample sizes. Since individual studies are usually underpowered in detecting the effect of low-penetrance genes, in this study we conducted a meta-analysis to investigate the association between GSTM1 null genotype and the risk for CAD.

Material and Methods

Publication search

We conducted a literature search before February 2014 in PubMed, EMBASE, and Chinese National Knowledge Infrastructure (CNKI) databases without restrictions. Combination of the following terms were applied: ‘coronary heart disease’ OR ‘coronary artery disease’ OR ‘myocardial infarction’ OR ‘acute coronary syndrome’ OR ‘ischemic heart disease’ OR ‘cardiovascular disease’ OR ‘major adverse cardiac event’ OR ‘CHD’ OR ‘CAD’ OR ‘MI’ OR ‘ACS’ OR ‘IHD’ OR ‘MACE’; ‘Glutathione S-transferases’ OR ‘GSTM1’; ‘polymorphism’ OR ‘variant’ OR ‘genetic’ OR ‘mutation’. We also conducted a manual search to find other articles based on references identified in the individual articles.

Inclusion criteria and data extraction

We included articles if they met all the following criteria: (1) evaluation of GSTM1 polymorphism and CAD risk, (2) using a case-control design, and (3) adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

Data were extracted by 2 authors independently. In case of conflicting evaluations, an agreement was reached following a discussion; if agreement could not be reached, another author was consulted to resolve the debate. The following information was extracted from each study: first author, year of publication, ethnicity, age, sex, disease type, sample size, smoking status, covariates, adjusted ORs, and the corresponding 95% CIs of CAD risk.

Results

Study characteristics

We ultimately identified a total of 13 articles reporting the relationship between GSTM1 null genotype and CAD risk [3–15]. A total of 5453 cases and 5068 controls were included in this meta-analysis. Table 1 summarized the main characteristics of those included studies. There were 8 case-control studies from white populations and 5 case-control studies from Asian populations.

Quantitative data synthesis

The evaluations of the association between GSTM1 polymorphism and CAD risk are summarized in Table 2. The null genotype of GSTM1 was associated with a significantly increased risk of CAD when compared with present genotype (adjusted OR=1.26; 95% CI 1.11–1.43; $I^2$=3%; Figure 1). When stratified by ethnicity, a significantly elevated risk was observed in whites (OR=1.22; 95% CI 1.06–1.41; $I^2$=0%) but not in Asians...
(OR=1.20; 95% CI 0.85–1.71;  P=50%). In the subgroup analysis according to disease type, a significantly increased myocardial infarction (MI) risk was observed (OR=1.19; 95% CI 1.01–1.40;  P=0%). Subgroup analysis of smoking status showed that increased risks were found in smokers (OR=1.97; 95% CI 1.59–2.44;  P=4%) but not in non-smokers (OR=1.20; 95%CI, 0.96–1.51;  P=20%). When we limited the meta-analysis to studies that controlled for confounders such as age, sex, smoking, diabetes, hypertension, family history, and dyslipidemia, a significant association between GSTM1 null genotype and CAD risk remained.

As shown in Figure 2, significant associations were evident with each addition of more data over time. The results showed that the pooled ORs tended to be stable. A single study involving in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs, and the corresponding pooled ORs were not materially altered (Figure 3).

Funnel plot and Egger’s test were performed to assess the publication bias of the literature. The shape of the funnel plot did not reveal any evidence of obvious asymmetry (data not shown). Egger’s test did not find evidence of publication bias ( P=0.68).

**Discussion**

The present meta-analysis, including 5453 cases and 5068 controls from 13 case-control studies, explored the associations of GSTM1 null genotype with CAD risk. We demonstrated that this polymorphism is significantly associated with an increased CAD risk. Subgroup analyses stratified by ethnicity showed whites, but not Asians, with GSTM1 null genotype had increased CAD risk. It was possible that different lifestyles, diets, and environments may account for this discrepancy. In the MI subgroup, we found that this polymorphism was associated with MI risk. Cigarette smoking is a pro-inflammatory stimulus and an important risk factor for CAD. Some studies

---

**Table 1. Characteristics of the case-control studies included in this meta-analysis.**

| First author | Year | Race   | Age | Sex | Type | Smoking | Case | Control | Covariate                                                                 |
|--------------|------|--------|-----|-----|------|---------|------|---------|----------------------------------------------------------------------------|
| Li           | 2000 | White  | 54  | Mixed| CAD  | Mixed*  | 400  | 890     | Age, sex, LDL, HDL, hypertension and diabetes                             |
| Masetti      | 2003 | White  | 61  | Mixed| CAD  | Mixed*  | 308  | 122     | Sex, dyslipidemia, hypertension, diabetes, and family history             |
| Girisha      | 2004 | Asian  | 47  | Mixed| CAD  | Mixed*  | 59   | 132     | Age, sex, smoke, alcohol, diet, cholesterol, triglyceride, HDL, LDL, VLDL, apoprotein B |
| Tamer        | 2004 | White  | 51  | Mixed| CAD  | Mixed*  | 148  | 247     | Smoke                                                                     |
| Cornelis     | 2007 | White  | 58  | Mixed| MI   | Mixed   | 2042 | 2042    | Smoke, waist-to-tip ratio, income, physical activity, history of diabetes and hypertension, intake of alcohol, and energy-adjusted saturated fat and folate |
| Manfredi     | 2007 | White  | 56  | Mixed| CAD  | Smoker  | 165  | 53      | Age, sex, dyslipidemia, hypertension, diabetes, and family history        |
| Kim          | 2008 | Asian  | 60  | Mixed| CAD  | Mixed*  | 582  | 110     | Age, sex, hypertension, diabetes, body mass index, and lipid profile     |
| Wang         | 2008 | Asian  | 62  | Mixed| CAD  | Mixed*  | 277  | 277     | Age, sex, smoke, dyslipidemia, hypertension, diabetes, body mass index     |
| Kariž        | 2012 | White  | 62  | Mixed| MI   | Mixed   | 206  | 257     | Age, sex, smoke, BMI, duration of diabetes and lipid parameters           |
| Lakshmi      | 2012 | Asian  | 58  | Mixed| CAD  | Mixed   | 352  | 282     | Age, sex, diabetes                                                       |
| Taspinar     | 2012 | White  | 62  | Mixed| CAD  | Mixed*  | 132  | 151     | Age, sex, smoke, diabetes and family history                             |
| Cora         | 2013 | Caucasian | 62  | Mixed| MI   | Mixed*  | 324  | 296     | Age, sex, smoke, diabetes, hypertension, family history and lipid profile |
| Yeh          | 2013 | Asian  | 64  | Mixed| CAD  | Mixed   | 458  | 209     | Age, sex, smoke, alcohol use, diabetes mellitus, levels of serum total cholesterol and high-density lipoprotein cholesterol |

* Information of smoking status can be extracted. CAD – coronary artery disease; MI – myocardial infarction; LDL – low-density lipoprotein; HDL – high-density lipoprotein; VLDL – very low-density lipoprotein; BMI – body mass index. 

---

© Med Sci Monit, 2014; 20: 1550-1555
have explored the interaction between \textit{GSTM1} genotype and smoking habits. Our results showed a significant association among smokers but not in non-smokers, suggesting that even the same variant in the same gene may have a different effect on the pathogenesis and occurrence of CAD in different individuals.

Previous studies have shown that individuals with \textit{GSTM1} null genotype have a decreased capacity to detoxify certain carcinogens. Thus, impaired \textit{GSTM1} function may lead to serious DNA damage. Toxic molecules produce DNA adducts that contribute to the development of atherosclerosis. Evidence indicates that the interaction of DNA adducts with DNA may trigger pathogenic pathways in the cell. Significant correlation was found between DNA adduct levels, which are accepted as a biomarker of exposure to environmental carcinogens, and atherogenic risk factors. Higher DNA adduct levels were detected in individuals with severe CAD [17,18] and in atherosclerotic plaques [19]. Therefore, it is biologically plausible that the \textit{GSTM1} null genotype may increase risk of CAD.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|}
\hline
 & Test of association & Heterogeneity & \\
 & OR (95\% CI) & \textit{P} value & \textit{P} value & \textit{I}^2 (\%) \\
\hline
Overall & 1.26 (1.11–1.43) & <0.01 & 0.41 & 3.0 \\
Asian & 1.20 (0.85–1.71) & 0.30 & 0.09 & 50.0 \\
Caucasian & 1.22 (1.06–1.41) & <0.01 & 0.97 & 0.0 \\
Mi & 1.19 (1.01–1.40) & 0.04 & 0.85 & 0.0 \\
Smoker & 1.97 (1.59–2.44) & <0.01 & 0.40 & 4.0 \\
Non-smoker & 1.20 (0.96–1.51) & 0.11 & 0.63 & 0.0 \\
\hline
Adjusted for & & & & \\
Age and sex & 1.31 (1.07–1.59) & <0.01 & 0.23 & 23.0 \\
Smoke & 1.29 (1.12–1.48) & <0.01 & 0.50 & 0.0 \\
Diabetes and hypertension & 1.31 (1.15–1.50) & <0.01 & 0.69 & 0.0 \\
Family history & 1.46 (1.07–1.99) & 0.02 & 0.50 & 0.0 \\
Dyslipidemia & 1.25 (1.03–1.51) & 0.03 & 0.32 & 13.0 \\
\hline
\end{tabular}
\caption{Results of meta-analysis.}
\end{table}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{forest_plot.png}
\caption{Forest plot for the association between CAD risk and \textit{GSTM1} null genotype.}
\end{figure}
Our study has some strengths. First, it was the first meta-analysis to report the adjusted ORs between GSTM1 null genotype and CAD risk. Second, the methodological issues for meta-analysis (e.g., subgroup analysis, cumulative meta-analysis, and sensitivity analysis) were well investigated. Third, when we limited the meta-analysis to studies that controlled for age and sex, smoking, diabetes and hypertension, family history, dyslipidemia, the significant positive association was only marginally altered. Finally, we did find significant heterogeneity and publication bias in this meta-analysis.

Some limitations in this meta-analysis should be addressed. First, the number of studies included in our meta-analysis remained small. Thus, publication bias may exist, although the funnel plots and Egger’s linear regression tests indicated no remarkable publication bias. Second, lack of the original data of the eligible studies limited the evaluation of the effects of the gene-environment interactions in CAD development. Third, no prospective studies have addressed this association between GSTM1 null genotype and CAD risk, and all included studies followed a retrospective case-control design. Thus, owing to the limitations of case-control design, we cannot exclude the possibility of undetected bias.

Conclusions

This meta-analysis supports an association between GSTM1 null genotype and risk of CAD. Prospective studies are suggested to further ascertain the relationship between GSTM1 null genotype and genetic predisposition to CAD.

Declaration of interest statement

The authors declare that they have no competing interests.
References:

1. Harrison D, Griendling KK, Landmesser U et al: Role of oxidative stress in atherosclerosis. Am J Cardiol, 2003; 91: 7–11

2. Jana S, Mandlekar S: Role of phase II drug metabolizing enzymes in cancer chemoprevention. Curr Drug Metab, 2009; 10: 595–636

3. Li R, Boerwinkle E, Olshan AF et al: Glutathione S-transferase genotype as a susceptibility factor in smoking-related coronary heart disease. Atherosclerosis, 2000; 149: 451–62

4. Masetti S, Botto N, Manfredi S et al: Interactive effect of the glutathione S-transferase genes and cigarette smoking on occurrence and severity of coronary artery risk. J Mol Med (Berl), 2003; 81: 488–94

5. Girisha KM, Gilmour A, Mastana S et al: T1 and M1 polymorphism in glutathione S-transferase gene and coronary artery disease in North Indian population. Indian J Med Sci, 2004; 58: 520–26

6. Tamer L, Ercan B, Camsari A et al: Glutathione S-transferase gene polymorphism as a susceptibility factor in smoking-related coronary artery disease. Basic Res Cardiol, 2004; 99: 223–29

7. Cornelis MC, El-Sohemy A, Campos H: GSTT1 genotype modifies the association between cruciferous vegetable intake and the risk of myocardial infarction. Am J Clin Nutr, 2007; 86: 752–58

8. Manfredi S, Federici C, Picano E et al: Glutathione S-transferase gene polymorphism as a susceptibility factor in smoking-related coronary artery disease. Basic Res Cardiol, 2004; 99: 223–29

9. Kim SJ, Kim MG, Kim KS et al: Impact of Glutathione S-Transferase M1 and T1 Gene Polymorphisms on the Smoking-Related Coronary Artery Disease. J Korean Med Sci, 2008; 23: 365–72

10. Wang LS, Tang JJ, Tang NP et al: Association of GSTM1 and GSTT1 gene polymorphisms with coronary artery disease in relation to tobacco smoking. Clin Chem Lab Med, 2008; 46: 1720–25

11. Karlí S, Nikolajević Starčević J, Petrović D: Association of manganese superoxide dismutase and glutathione S-transferases genotypes with myocardial infarction in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract, 2012; 98: 144–50

12. Lakshmi SV, Naushad SM, Saumya K et al: Role of CYP1A1 haplotypes in modulating susceptibility to coronary artery disease. Indian J Biochem Biophys, 2012; 49: 349–55

13. Taspinar M, Aydos S, Sakiragaoglu O et al: Impact of genetic variations of the CYP1A1, GSTT1, and GSTM1 genes on the risk of coronary artery disease. DNA Cell Biol, 2012; 31: 211–18

14. Yeh HL, Kuo LT, Sung FC et al: GSTM1, GSTT1, GSTP1, and GSTA1 genetic variants are not associated with coronary artery disease in Taiwan. Gene, 2013; 523: 64–69

15. Egger M, Smith GD, Schneider M et al: Bias in meta-analysis detected by a simple, graphical test. BMJ, 1997; 315: 6296–34

16. De Flora S, Izzotti A, Walsh D et al: Molecular epidemiology of atherosclerosis. FASEB J, 1997; 11: 1021–103

17. Van Schooten FJ, Hirvonen A, Maas LM et al: Putative susceptibility markers of coronary artery disease: association between VDR genotype, smoking and aromatic DNA adduct levels in human right atrial tissue. FASEB J, 1998; 12: 1409–17

18. Ross R: The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature, 1993; 362: 801–9