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Genetic polymorphism of N142D *GSTO2* and susceptibility to breast cancer: a meta-analysis

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ABSTRACT

To establish a comprehensive picture of the relationship between glutathione S-transferase omega 2 (*GSTO2*; MIM: 612314) gene N142D variant (rs. 156697) and breast cancer risk, the present meta-analysis was carried out. Studies published up to July 2012 with information about *GSTO2* polymorphism and breast cancer risk were identified using several electronic databases. We identified 4 eligible studies, including 2678 subjects (1316 patients, and 1362 healthy controls) in relation to the N142D polymorphism of *GSTO2* and risk of breast cancer. There was no heterogeneity between studies. Considering all of the studies, the DD (OR=1.29, 95%CI: 0.99-1.67, P=0.055) and ND (OR=1.03, 95%CI: 0.88-1.21, P=0.697) genotypes, did not alter the risk of breast cancer in comparison with the NN genotype. Therefore, it is suggested that if the number of studies increased, finding a significant association between N142D polymorphism of *GSTO2* and susceptibility to breast cancer would be very probable.

Key words: Breast Cancer; Meta-analysis; *GSTO2*; Susceptibility

INTRODUCTION

Glutathione S-transferases (GSTs; EC 2.5.1.18) belong to an enzyme superfamily which participates in phase II of detoxification. The GSTs are divided into several classes including class omega (*GSTO*). The glutathione S-transferase omega 2 (*GSTO2*; MIM: 612314) gene contains 6 exons and spans 24.5 kb. The human *GSTO2* is a protein with 243 amino acid residues. The *GSTO2* has poor activity with common GST substrates, and exhibits novel enzyme activities including glutathione-dependent thioltransferase, dehydroascorbate reductase, and monomethylarsonate reductase activities [1].

In human beings, the *GSTO2* is polymorphic with the A>G transition at nucleotide position 424 in exon 4 of *GSTO2* (db SNP rs. 156697). This variation causes an Asn142Asp (N142D) substitution [1]. There is evidence indicating that this substitution may alter the function of the *GSTO2* enzyme [2, 3]. The 142D allozyme is expressed at approximately 80% of the 142N allozyme level [2].

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During the past years, several studies have investigated the association between N142D polymorphism of *GSTO2* and susceptibility to several types of cancers [4-11]. The gene encoding *GSTO2* has already been mapped on human chromosome 10q24-q25 [1]. Of the particular interest, cytogenetic alterations of human 10q have been associated with breast cancer [12-15]. Therefore, it is quite probable that *GSTO2*, plays at least a partial role as a low-penetrance gene in the development of breast cancer.

There were studies investigating the association between N142D polymorphism of *GSTO2* and susceptibility to breast cancer [8-11]. Although the reported ORs were higher than 1.1, there was no significant association. This could be partly due to the insufficient powers of the studies and the small effect of N142D polymorphism of low-penetrance *GSTO2* gene on breast cancer risk. We therefore, performed a meta-analysis of the published studies to establish a comprehensive picture of the relationship between *GSTO2* N142D variant and breast cancer risk.

MATERIALS AND METHODS

Search strategy for meta-analysis: Studies published up to July 2012 with information about *GSTO2* polymorphism and breast cancer risk were identified using electronic databases, MEDLINE (National Library of Medicine, Washington, DC, USA), Scopus, EBSCOhost Research Databases, ProQuest, Scirus, DOAJ (Directory of Open Access Journals), Indian Science Abstract, Google Scholar, SAGE, Open J-Gate, High-Wire, J-STAGE, JSTOR, VT Libraries, ASCI (Asian Science Citation Index), and SID (Scientific Information Database). The search terms were "breast cancer", polymorphism and *GSTO2*. Furthermore, references cited in the retrieved articles were reviewed to trace additional relevant studies.

Inclusion criteria and data extraction: The meta-analysis was limited to published articles in English. Selected articles for meta-analysis had no subject overlap with other studies. Articles describing case-control design studies and their primary references were selected for analysis.

All studies were reviewed twice and the data was extracted using a standardized form. Data were collected on the authors, year of publication, country of origin, study design, source of control group (hospital based, population based), ethnicity and numbers of *GSTO2* genotypes among cases and controls.

Statistical analysis: For the control group of each study, the observed frequencies of *GSTO2* genotypes were assessed for the Hardy-Weinberg equilibrium using the χ^2 statistic. Odds ratios (ORs) and their corresponding 95% confidence intervals (CI) of breast cancer associated with the polymorphism of N142D *GSTO2* were calculated for each comparison. In comparison, the 142N and/or NN genotype were assumed as the reference group.

To take into account the possibility of heterogeneity across the studies, an analysis of heterogeneity was performed using a Q statistical test, in which a P-value greater than 0.05 suggested significant heterogeneity between the studies [16]. The association was measured using random-effect or fixed-effect models according to the heterogeneity of the studies. Fixed-effect and random-effect methods were used by Mantel-Haenszel [17] and DerSimonian and Laird methods [16], respectively.

RESULTS

In the present meta-analysis 4 eligible studies were identified [8-11], including 2678 subjects (1316 patients, and 1362 healthy controls) in relation to the N142D polymorphism of *GSTO2* and risk of breast cancer (Table 1).

Table 1: Studies used in the meta-analysis

Study (year)	Place	Genotypes of Controls				Genotypes of Cases		
		NN	ND	DD	HWE*	NN	ND	DD
Marahatta et al., 20006	Thailand	21	11	1	0.095	19	10	1
Chariyalertsak et al., 2009	Thailand	86	60	5	2.024	59	38	4
Masoudi et al., 2010	Iran	80	78	23	0.328	74	75	32
Andonova et al., 2011	Germany	442	453	102	0.799	425	456	123

Note: * χ^2 for testing the Hardy-Weinberg equilibrium. In all studies $P > 0.05$

The *GSTO2* N142D genotypic frequencies in all of the subjects of the control groups were in the Hardy-Weinberg equilibrium. Using the Q statistical test [17], it was found that there was no heterogeneity between the studies (for ND vs NN comparison: Q statistic=0.200, df=3, P=0.978; for DD vs NN comparison: Q statistic=0.303, df=3, P=0.960); therefore, the association was measured using a fixed-effect model. Considering all of the studies carried out up to July 2012, the DD (OR=1.29, 95%CI: 0.99-1.67, P=0.055) and ND (OR=1.03, 95%CI: 0.88-1.21, P=0.697) genotypes did not alter the risk of breast cancer in comparison to the NN genotype. Taken into account the allelic frequency of the polymorphism, there was no heterogeneity between these studies (Q statistic=0.629, df=3, P=0.890) and the D allele did not alter the risk of breast cancer, in comparison to the N allele (OR=1.09, 95%CI: 0.97-1.23, P=0.111).

Because of the small number of studies, the effects of ethnicity, source of the control group, and sample size could not be explored.

Table 2: Genetic polymorphism of *GSTO2* N142D and breast cancer risk

Study (year)	Ref.	ND vs NN			DD vs NN			D vs N		
		OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Marahatta et al., 20006	8	1.01	0.34-2.89	0.993	1.11	0.07-18.9	0.945	1.01	0.42-2.44	0.966
Chariyalertsak et al., 2009	9	0.92	0.54-1.55	0.765	1.16	0.30-4.52	0.824	0.97	0.64-1.49	0.915
Masoudi et al., 2010	10	1.04	0.66-1.62	0.865	1.50	0.80-2.80	0.198	1.19	0.88-1.62	0.247
Andonova et al., 2011	11	1.04	0.86-1.26	0.629	1.25	0.93-1.68	0.132	1.09	0.96-1.24	0.179
Meta-analysis		1.03	0.88-1.21	0.697	1.29	0.99-1.67	0.055	1.09	0.97-1.23	0.111
Q statistic			0.200			0.303			0.629	
P-value (df=3)			0.978			0.960			0.890	

DISCUSSION

There were 4 published studies in scientific journals related to the N142D polymorphism of *GSTO2* and risk of breast cancer [8-11]. These studies are limited by small sample sizes, therefore, meta-analysis in pooling these studies gains significance, particularly when detecting small effect sizes that may be associated with polymorphism.

The present meta-analysis revealed that there was no heterogeneity between the studies. Including all studies, ND genotype did not alter the risk of breast cancer in comparison with the NN genotype (Table 2). However, the association between DD vs NN genotypes was found to increase the risk of breast cancer but not significantly ($P=0.055$, Table 2).

It should be mentioned that the major limitation of the present study was the small number of articles ($n=4$) and consequently the small sample size in both breast cancer patients and controls available for meta-analysis. It is suggested that if the number of studies increased, finding a significant association between N142D polymorphism of *GSTO2* and susceptibility to breast cancer would be very probable. In order to test this hypothesis, more studies will be needed. Possible association between some polymorphisms with an altered risk of some types of cancers has been previously reported only in a specific ethnic group [18-23]. Therefore, more studies on different ethnic groups seem to be necessary. However, before that, it is suggested that the results be interpreted with caution.

It is reported that genetic polymorphisms, in relation to each other or to known risk factor(s), have additive effects on the risk of multi-factorial traits [18, 21, 24-26]. It has been reported previously that *GSTO2*, *XRCC1* has an additive effect on the risk of breast cancer [18]. For future investigations, studying the additive effect of this polymorphism with other polymorphisms and/or with other known breast cancer risk factors, such as family history in first relatives, is recommended.

Acknowledgments

The author is indebted to Dr. Maryam Ansari-Lari for critical reading of the manuscript and for her contribution in discussions. This study was supported by Shiraz University.

Conflict of Interest: Author has no financial or any non-financial competing interests.

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