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GSTM1, GSTT1 Null Variants and GPX1 Single Nucleotide Polymorphism Are Not Associated With Bladder Cancer Risk in Egypt

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Abstract

Background—Bladder cancer is the most common male malignancy in Egypt, consists predominantly of urothelial cell (UC) and squamous cell (SCC) carcinoma, and disparities in incidence exist between men and women regardless of geographic region. Tobacco smoke exposure and *Schistosoma haematobium* (SH) infection and the presence of GSTM1, GSTT1, and GPX1 genotypes, as modulators of the carcinogenic effect of reactive oxidative species (ROS), were hypothesized to modify bladder cancer risk and possibly explain these gender differences.

Methods—We evaluated the association between bladder cancer risk and functional polymorphisms in the GSTM1, GSTT1, and GPX1 genes in 625 cases and 626 matched population-based controls in Egypt, and assessed for potential interactions between these candidate genes and environmental exposures such as smoking and SH. We analyzed the risk for UC and SCC separately.

Results—None of these functional polymorphisms were significantly associated with bladder cancer risk. There were no significant interactions between genotypes and smoking or SH in this population, nor was any difference detected in genotypic risk between men and women.

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Conclusions—Our findings suggest that common genetic variations in GSTM1, GSTT1, and GPX1 are not associated with bladder cancer risk overall, and that well known environmental risk factors, such as smoking and SH do not interact with these genes to modulate the risk.

Impact—Our data indicate that common genetic variations in GSTM1, GSTT1, and GPX1 were not associated with bladder cancer risk.

Keywords

GSTM1; GSTT1; GPX1; bladder cancer; epidemiology

Introduction

Bladder cancer is the most common male malignancy in Egypt and disparities in incidence exist between men and women regardless of geographic region, with a world age-standardized incidence rate of 10.1 per 100,000 persons-years for men and 2.5 per 100,000 persons-years for women (1). Tobacco smoke exposure and *Schistosoma haematobium* (SH) infection are established risk factors for bladder cancer. In Egypt, smoking is much more prevalent among adult males (22% - 47%) than females (2% - 7%) (2), but smoking has not been shown to fully account for the observed gender differences in bladder cancer incidence (1). A common pathway of bladder carcinogenesis for both tobacco smoke and SH infection may be the cellular response to oxidative stress and inflammation, and several genes, including glutathione-S-transferase (GST) and glutathione peroxidase (GPX), are thought to be involved in the mediation of the toxicity of reactive oxygen species (ROS). A number of studies have investigated the association between GSTM1, GSTT1 and GPX1 variant genotypes and increased bladder cancer risk, including interactions with smoking, SH and gender; however, with conflicting results. In the present study, polymorphisms in GSTM1, GSTT1, and GPX1 genes were hypothesized to modify bladder cancer risk and possibly explain these gender differences.

Materials and Methods

Study population

Adult urinary bladder cancer cases (n = 625) were recruited within 1 year of diagnosis and non- cancer controls (n=626) were recruited as previously described (3). Cases were confirmed by pathological examination and defined as urothelial (transitional) cell (UC), squamous cell (SCC), adenocarcinoma, or other types of carcinoma of the bladder. We included only those with UC and SCC (95% of the cases) in this analysis. After informed consent, cases and controls were administered a detailed questionnaire that included questions of sociodemographic characteristics, smoking history, and medical history including a history of schistosomiasis.

Laboratory analyses

GSTM1 null, GSTT1 null, and GPX1 rs1050450 genotypes were determined using TaqMan allelic discrimination assays (Applied Biosystems) with a successful genotyping rate of ≥99.0% and genotype concordance (among 10% blind quality control duplicates) of ≥99.0%.

Statistical analyses

Odds ratios (OR) and 95% confidence intervals (CI) were used to estimate associations between each genotype and bladder cancer risk. The estimates were obtained from unconditional logistic regression analysis, adjusting for sex, age, region of residence,

tobacco smoking, and schistosomiasis. After the initial analysis of all cases combined, separate models were created for UC and SCC, and stratified by gender, tobacco smoking in men (ever vs. never), and self-reported history (yes/no) of schistosomiasis. In instances where the number of exposed subjects was <10 for any of the above comparisons, we used exact methods to estimate the OR and 95% CI. All statistical analyses were done using SAS version 9.2 (SAS Institute Inc.). The genotype distributions of all three polymorphisms were in Hardy-Weinberg equilibrium (HWE) in control subjects, calculated using Pearson's goodness of fit test.

Results

Table 1 shows the frequency distribution of the demographic variables and putative risk factors of bladder cancer. We found no statistically significant association between bladder cancer risk for both UC and SCC (in men and women combined) and the GSTM1 null variant (OR = 0.94, 95% CI = 0.74 - 1.18), GSTT1 null variant (OR = 1.09, 95% CI = 0.83 - 1.42), and GPX1 T/T genotype (OR = 1.02, 95% CI = 0.64 – 1.64) (Table 2). In addition, no statistically significant associations were observed for UC or SCC separately. Similarly, we found no significant interactions between genotypes and smoking, SH or gender (data not shown).

Discussion

We found no statistically significant association between bladder cancer risk and functional polymorphisms in the GSTM1, GSTT1, and GPX1 genes, and no significant interactions between genotypes and smoking, SH or gender.

Previous studies have found that the GSTM1 null genotype is associated with an increased risk of bladder cancer overall, among SH-infected individuals (4), and among male smokers (5). Conversely, other studies have reported increased risk in women but not men, and among women, only among smokers (6), as well as no overall association with increased risk (7). Associations between the GSTT1 null variant and overall increased risk were reported by some investigators (7) but not others (6), and among women but not men (7). Similarly, studies of the association of the variant GPX1 genotype with bladder cancer reported inconsistent findings (8, 9).

One possible explanation for the inconsistencies in findings of prior and current studies is that they could reflect differences in gene-environment interactions in different populations. Another possibility is differences in laboratory methods (e.g., RFLP may have a higher rate of false positives vs. TaqMan).

In conclusion, our results suggest that common genetic variations in GSTM1, GSTT1, and GPX1 are not associated with overall bladder cancer risk.

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Table 1

Distribution of demographic variables and risk factors of bladder cancer

	Cases				Controls	
	UC		SCC			
	No.	%	No.	%	No.	%
Total	389	62	236	38	626	
Females	55	14.1	67	28.4	195	31.2
Males	334	85.9	169	71.6	431	68.8
Smoking (males only)						
Never smokers	71	21.3	49	29.0	145	33.6
Smokers	263	78.7	120	71.0	286	66.4
Schistomiasis						
Never infected	165	42.4	110	46.6	354	56.5
Infected	198	50.9	108	45.8	236	37.7
Undetermined	26	6.7	18	7.6	36	5.8

Table 2

Bladder cancer risk associated with GSTM1, GSTT1, and GPX1 polymorphisms

	UC + SCC				UC				SCC			
	Cases	Controls	OR[1]	(95% CI)	Cases	Controls	OR[1]	(95% CI)	Cases	Controls	OR[1]	(95% CI)
GSTM1												
+	274	289	1.00	(Ref.)	162	289	1.00	(Ref.)	112	289	1.00	(Ref.)
-	344	332	0.94	(0.74 - 1.18)	223	232	0.77	(0.59 - 1.03)	121	332	1.16	(0.85 - 1.57)
GSTT1												
+	470	464	1.00	(Ref.)	290	464	1.00	(Ref.)	180	464	1.00	(Ref.)
-	147	156	1.09	(0.83 - 1.42)	96	156	0.95	(0.69 - 1.32)	51	156	1.25	(0.86 - 1.81)
GPX1												
CC	330	326	1.00	(Ref.)	196	326	1.00	(Ref.)	134	326	1.00	(Ref.)
CT	236	254	0.91	(0.72 - 1.17)	149	254	1.01	(0.74 - 1.36)	87	254	0.86	(0.62 - 1.18)
TT	46	38	1.02	(0.64 - 1.64)	35	38	1.28	(0.75 - 2.19)	11	38	0.70	(0.34 - 1.43)

[1] Adjusted for sex, age, region of residence, tobacco smoking, and schistosomiasis.

For GSTM1 and GSTT1 “+” indicates heterozygous or homozygous carriers of the wild-type allele, “-” indicates homozygous carriers of the null allele. Numbers do not sum to to the total samples available because of missing genotype data.