GSTM1 and GSTT1 genes null polymorphisms in kidney cancer susceptibility: evidence based on a meta-analysis

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Abstract

Introduction: Renal cancer is a complex and multifactorial oncourologic disease. **Objective:** To conduct a meta-analysis in order to investigate the association of *GSTM1* and *GSTT1* genes null polymorphisms in renal cancer. **Method:** Case-control studies in humans, published from 1999 to 2013, that investigated the association of *GSTM1* and *GSTT1* genes null polymorphisms in renal cancer were grouped in order to make of this meta-analysis. **Results:** Ten articles were selected on the subject proposed. No associations were found between polymorphisms of *GSTM1*-null (OR = 1.015, 95% CI = 0.897 to 1.147) and *GSTT1*-null (OR = 1.081, 95% CI = 0.791 to 1.479) and renal cancer. **Conclusions:** Based on the results obtained, we conclude that the *GSTM1* and *GSTT1* null polymorphisms are not associated with the risk of developing renal cancer, since they have limited role, if there is any on effective contribution in the development of renal tumors.

Keywords: kidney neoplasms; meta-analysis; polymorphism, genetic.

Introduction

Renal cancer is a complex multifactorial urologic disease.[1] It encompasses a series of malignant tumors with genetic polymorphisms affecting the kidneys.[2] In this context, different types of kidney tumor produce significantly diverse histopathology findings and genetic alterations involving various molecular pathways, in addition to yielding multiple clinical manifestations and treatment options.[3]

The incidence of renal cell carcinoma - the most common form of renal cancer - is increasing globally,[4] and currently ranks third among genitourinary tract tumors.[5] Renal cell carcinoma accounts for approximately three percent of all cases of malignant tumors in adults, with over 270,000 new cases and more than 100,000 deaths a year.[6-8]

The risk factors for the development of renal cancer include smoking, obesity, hypertension, diabetes mellitus type 2[7] and genetic factors.[9] In the last decades, the genes in charge of coding hepatic xenobiotic metabolizing enzymes such as glutathione S-transferases (GST) have gained prominence in oncogenetics. Genetic polymorphisms in GST have also earned a special place in cancer research, including renal cell carcinoma.[10]

Human GST can be divided into two distinct superfamilies, linked to microsomal and cytosolic proteins. Cytosolic GSTs are subject to genetic polymorphisms in human populations. Human genes are divided into six classes, two of which are the Mu class, present in the GSTM1 gene on chromosome 1p13.3, and the Theta class, found in the GSTT1 gene in chromosome 22q11.23.[11]

Genetic polymorphisms categorized as null result from genetic deletions. In this context, the following allelic possibilities may be observed:

(1) homozygous dominant subjects with two functional alleles (GST+/GST+), (2) heterozygous individuals with only one functional allele (GST+/GST-), or (3) homozygous recessive individuals without functional alleles (GST-/GST-).[12] Thus, homozygous recessive individuals with a GST null genotype are not capable of producing the GST protein variant affected by the deletion, which usually places them at risk for the development of many types of cancer, particularly when exposed to carcinogenic substances.[10]

GSTM1 and GSTT1 null polymorphisms have been the subject of several case-control studies on renal cell carcinoma.[10] Interestingly, the conclusions reported in these studies varied significantly, with some authors describing absence and others presence of associations between GSTM1 and GSTT1 null polymorphisms and kidney cancer. This generalized lack of agreement motivated the organization of the present study, a meta-analysis designed to investigate the association between GSTM1 and GSTT1 null polymorphisms and kidney cancer.

Method

This study is a meta-analysis. The purpose of a meta-analysis is to examine the combined outcomes of several studies on the same topic.[13] This type of study is widely used in medical sciences, once the aggregation of the data derived from numerous studies on the same subject increases the level of confidence of the ensuing statistical inferences.[14] A meta-analysis may be carried out to underline the agreement existing between studies on a particular topic, or to stress disagreements between studies, thus indicating the need for further joint analysis to strengthen the existing conclusions on the matter at hand.[15] The main steps of a meta-analysis are: (1) bibliographic search, (2) processing the outcomes of each selected study into a common indicator, (3) assessing the homogeneity of the outcomes, (4) modeling the variation between studies, and (5) assessing sensitivity.[16]

Relevant human studies published between 1999 and 2013 were identified in the SciELO database (Scientific Electronic Library Online) and on the NCBI (National Center for Biotechnology Information, USA) PubMed. The search for papers included combinations of keywords "polymorphism," "GSTM1 and GSTT1 genes," and "kidney or renal cancer." Ten papers on GSTM1 and GSTT1 null polymorphisms and kidney cancer were included in the meta-analysis.

In a meta-analysis, it is important to assess the heterogeneity of the included studies. Design and method differences may pose significant challenges to the aggregation of study results.[17] Heterogeneity may be typified into three categories: clinical, methodological, and statistical. In order to minimize the impact of these parameters, inclusion and exclusion criteria are broadly defined.[18] The papers included in the present study had to meet the following inclusion/exclusion criteria: case-control studies enrolling humans published between 1999 and 2013 on the association between GSTM1 and GSTT1 null polymorphisms and kidney cancer. The following data were collected: site of the study; first author's name; year of publication of the paper; total number of cases and controls; and genotypic frequency of GSTM1 and GSTT1 null polymorphisms. The studies included in this meta-analysis looked into patients with histologically confirmed renal cell carcinoma and polymorphisms detected with PCR.

Heterogeneity - defined as the diversity between studies - may significantly affect the results. Diversity can be assessed using the χ^2 test for heterogeneity.[13] The genotype frequencies reported in the papers included in this meta-analysis were grouped in a single table and diversity was assessed with the χ^2 test for heterogeneity in 2x2 contingency tables, to compare between the different odds ratios (OR) with a 95% confidence interval described in each study.[16]

The null hypothesis was confirmed for p-values > 0.05, i.e., the compared studies were homogeneous. In such case, a fixed-effect model is used, in which the studies are assumed to point in the same direction.[19] In this context, the Mantel-Haenszel test is the most commonly used method.[20] On the other hand, if the χ^2 test for heterogeneity yields a p-value < 0.05, the compared studies are diverse and heterogeneous. In this scenario, random effect methods[21] such as the DerSimonian Laird estimator [15,22] are recommended.

Global association tests were then used to assess the significance of the correlation between GSTM1 and GSTT1 null polymorphisms and kidney cancer in the included studies combined. The impact these polymorphisms in the development of renal cell carcinoma was assessed using a fixed-effect model for gene GSTM1 (p = 0.678) and a random-effect model for gene GSTT1 (p = 0.0002) using software package BioEstat® 5.0.[20]

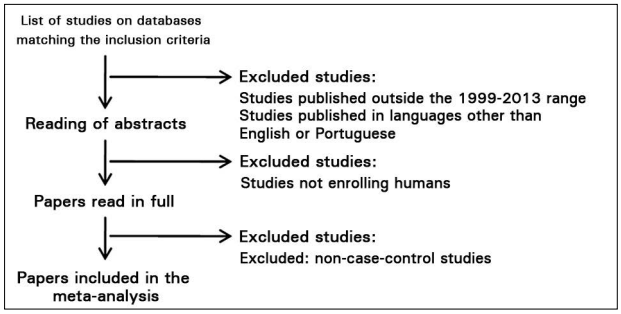
Odds ratios, 95% confidence intervals, and the weights attributed to each study individually and combined for both fixed-effect and random-effect models were calculated to estimate the global impact of the polymorphisms. Studies with greater statistical power, i.e., with larger enrolled populations and greater intervention effects, were given greater weights.[18] These tests yield forest plots, which allow the summarization of all the information on the effect and contribution of each study to the analysis.[13]

Results

This meta-analysis included ten papers on the association between GSTM1 and GSTT1 null polymorphisms and kidney cancer, published between 1999 and 2013. Five papers were excluded for not containing control groups.[23-26] Only studies meeting the inclusion and exclusion criteria were considered (Figure 1).[27-36]

A total of 9,188 genotyping tests for GSTM1 and GSTT1 null polymorphisms were carried out. Tests for GSTM1 polymorphisms were performed in 4,595 individuals, 1,717 (37.4%) diagnosed with kidney cancer (cases) and 2,878 (62.6%) healthy subjects (controls).

Figure 1. Criteria for the identification, inclusion, and exclusion of studies in the meta-analysis.



Tests for GSTT1 polymorphisms were performed in 4,593 individuals, 1,720 (37.4%) with kidney cancer and 2,873 (62.6%) healthy subjects. Gene GSTM1 was found in 857 (49.9%) and not found in 860 (50.1%) individuals diagnosed with cancer; 1,279 (74.4%) patients were positive and 441 (25.6%) were negative for gene GSTT1.

Among controls, 1,442 (50.1%) individuals were positive and 1,436 (49.9%) negative for gene GSTM1, while 2,031 (70.7%) were positive and 842 (29.3%) were negative for gene GSTT1. Data on GSTM1 and GSTT1 genotyping tests are shown in Tables 1 and 2, respectively.

The group of patients with renal cancer ranged from 44 with both genes[36] to 624 individuals with gene GSTM1 and 628 with gene GSTT1.[31] The control group ranged from 14 individuals with both genes[36] to 887 with gene GSTM1 and 913 with gene GSTT1.[31]

No associations were found between GSTM1 (OR = 1.015; 95% CI 0.897-1.147) and GSTT1 (OR = 1.081; 95% CI 0.791-1.479) null polymorphisms and kidney cancer.

In the forest plots generated in the meta-analysis, each line represented a different study. The rhombus at the bottom of the diagram represented the combination of results of the studies included in the meta-analysis. The result of each study is given in graphic and numerical form. In the graphic representations, the central squares account for relative risk (RR) or hazard ratios, while the lines account for confidence intervals (CI). When the CI does not cross the null line (position 1.0 in the graph), the study is deemed

Table 1 Analysis of GSTM1 null polymorphism in cases and controls, papers published between 1999 and 2013

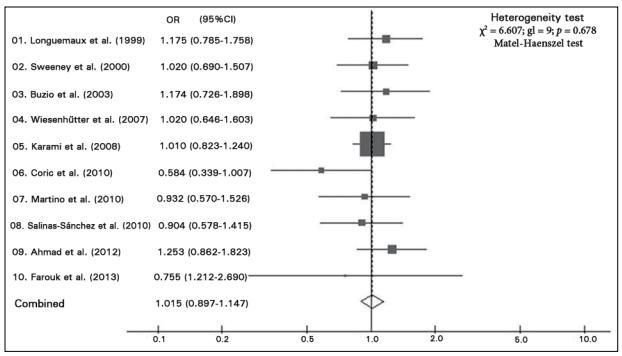
N	Author	Year	Site	Case					Controle					OR	95% CI	
				GSTM1 +		*GSTM1* -		Total	*GSTM1* +		*GSTM1* -		Total		Lower Limit	Upper Limit
				n	f (%)	n	f (%)		n	f (%)	n	f (%)				
1	Longuemaux	1999	France	84	48.6	89	51.4	173	94	44.5	117	55.5	211	1.175	0.785	1.758
2	Sweeney	2000	USA	63	50.0	63	50.0	126	250	49.6	255	50.6	505	1.020	0.690	1.507
3	Buzio	2003	Italy	50	30.3	50	30.3	100	92	46.0	108	54.0	200	1.174	0.726	1.898
4	Wiesenhütter	2007	Germany	51	52.0	47	48.0	98	167	51.5	157	48.5	324	1.020	0.646	1.603
5	Karami	2008	Europe	321	51.1	303	48.2	624	454	49.7	433	47.4	887	1.010	0.823	1.240
6	Coric	2010	Serbia	30	39.5	46	60.5	76	96	52.7	86	47.3	182	0.584	0.339	1.007
7	Martino	2010	Austria	67	45.6	80	54.4	147	53	47.3	59	52.7	112	0.932	0.570	1.526
8	Salinas-Sánchez	2010	Spain	76	57.6	57	43.2	133	115	70.6	78	47.9	193	0.904	0.578	1.415
9	Ahmad	2012	India	102	52.0	94	48.0	196	116	46.4	134	53.6	250	1.253	0.862	1.823
10	Farouk	2013	Egypt	13	29.5	31	70.5	44	5	35.7	9	64.3	14	0.755	1.212	2.690
Combined				857	49.9	860	50.1	1,717	1,442	50.1	1,436	49.9	2,878	1.015	0.897	1.147

Table 2 Analysis of GSTT1 null polymorphism in cases and controls, papers published between 1999 and 2013

N	Author	Year	Site	Case					Control					OR	95% CI	
				GSTT1 +		*GSTT1* -		Total	*GSTT1* +		*GSTT1* -		Total		Lower Limit	Upper Limit
				n	f (%)	n	f (%)		n	f (%)	n	f (%)				
1	Longuemaux	1999	France	148	85.5	25	14.5	173	171	81.0	40	19.0	211	1.375	0.800	2.365
2	Sweeney	2000	USA	90	71.4	36	28.6	126	411	81.5	93	18.5	504	0.563	0.361	19.390
3	Buzio	2003	Italy	89	89.0	11	11.0	100	165	82.5	35	17.5	200	1.669	0.818	3.406
4	Wiesenhütter	2007	Germany	19	19.4	79	80.6	98	59	18.2	265	81.8	324	1.094	0.619	1.934
5	Karami	2008	Europe	499	79.5	129	20.5	628	752	82.4	161	17.6	913	0.828	0.640	1.071
6	Coric	2010	Serbia	55	72.4	21	27.6	76	130	71.4	52	28.6	182	1.038	0.574	1.877
7	Martino	2010	Austria	120	81.6	27	18.4	147	89	79.5	23	20.5	112	1.151	0.622	2.128
8	Salinas-Sánchez	2010	Spain	110	83.3	22	16.7	132	138	84.7	25	15.3	163	0.904	0.487	1.680
9	Ahmad	2012	India	125	63.8	71	36.2	196	106	42.4	144	57.6	250	2.382	1.623	3.494
10	Farouk	2013	Egypt	24	54.5	20	45.5	44	10	71.4	4	28.6	14	0.512	0.147	1.789
Combinado				1,279	74.4	441	25.6	1.720	2,031	70.7	842	29.3	2,873	1.081	0.791	1.479

statistically significant, either separately or combined. The larger the sample considered in the study, the narrower the confidence intervals and the greater the areas of the squares, denoting more accurate results and greater contribution to the meta-analysis.[18] Two graphs were generated, one for gene GSTM1 (Figure 2) and another for gene GSTT1 (Figure 3).

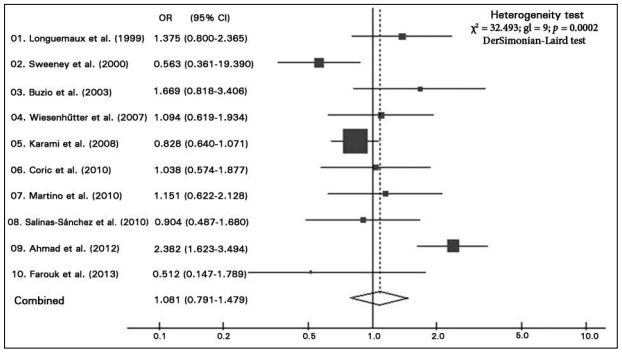
Figure 2. Odds ratios (OR) and 95% confidence interval (95% CI) with lower and upper limits, for GSTM1 null polymorphism in all studies with non-significant chi-square test for heterogeneity (Mantel-Haenszel test).



Discussion

Mixed results were reported in the studies on GSTM1 and GSTT1 null polymorphisms in patients with various tumor types. Lack

Figure 3. Odds ratios (OR) and 95% confidence interval (95% CI) with lower and upper limits, for GSTT1 null polymorphism in all studies with significant chi-square test for heterogeneity (DerSimonian-Laird estimator).



of a correlation with polymorphisms was reported in cases of lung cancer[37] and renal cell carcinoma.[24-26,29,38] Other authors suggested the existence of associations with one or both polymorphisms in cases of head and neck tumors,[39] prostate cancer,[40] breast cancer,[41] cervical cancer,[42] and hepatocellular carcinoma.[43]

Several meta-analyses have looked into the involvement of GSTM1 and GSTT1 null polymorphisms in various tumor types.

Gong *et al.*[40] published a meta-analysis investigating the association between GSTM1 and GSTT1 null polymorphisms and prostate cancer and concluded that individuals with a GSTM1-null genotype or null genotypes for both genes were at higher risk of developing prostate cancer. On the other hand, the GSTT1-null genotype alone was not significantly associated with onset of prostate cancer. Liu *et al.*,[44] in another meta-analysis, reached similar conclusions.

The authors of another meta-analysis[42] assessed GSTM1 and GSTT1 null polymorphisms in cases of cervical cancer and concluded that null genotypes alone or together were associated with significantly increased risk of developing the disease. The same study also evaluated two interactions between the genes and environmental factors such as smoking and HPV infection, but the authors did not find associations between the analyzed polymorphisms and environmental factors.

A more recent meta-analysis[43] including studies performed with Chinese populations investigated the association between susceptibility to hepatocellular carcinoma and GST null polymorphisms. The authors suggested that Chinese populations with GSTM1 and GSTT1 null polymorphisms were at higher risk of developing hepatocellular carcinoma.

A meta-analysis by Tang *et al.*[45] looked into the impact of null polymorphisms of the main GSTs in the development of acute leukemia in children. The authors associated GSTM1 null polymorphism with increased risk of developing pediatric acute leukemia, although an equal association was not reported for GSTT1-null genotypes.

In a meta-analysis similar to ours, Yang *et al.*[10] reviewed cases of null polymorphism in three GST genes: GSTM1, GSTT1, and GSTP1. The conclusions the authors reported were similar to the ones described in this meta-analysis, i.e., no association was found between null polymorphisms in these three genes and risk of developing renal cell carcinoma. Another meta-analysis on the same topic failed to find associations with isolated polymorphisms, but the analysis of the interaction between GSTM1 and GSTT1 revealed significant associations between the double-null genotype and renal cancer.[46] A meta-analysis by Liu *et al.*[47] found no associations between GSTM1 null polymorphism and renal cancer.

In general terms, meta-analyses face important limitations as they attempt to group studies carried out in different places, at different times, using different methods. The number of studies pooled for the purposes of a meta-analysis may also be a relevant limitation. A meta-analysis with a greater number of studies is likely to yield more reliable results and conclusions. In contrast, when few studies are compiled for analysis, a roster of issues such as poor ethnic representation and lack of relevant oncologic variables - environmental exposure, patient habits etc. - may also arise.

Conclusion

The results of this meta-analysis suggest that GSTM1 and GSTT1 null polymorphisms are not

associated with risk of developing kidney cancer. The polymorphisms analyzed in this study appear to have a limited role, if any, in the development of renal tumors. Considering the significant increase in the number of studies on the topic and the growing knowledge on variables relevant to renal cancer care, other meta-analyses should be organized to strengthen the pool of statistical data and address discordant findings.

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