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Genotype association *GSTM1* null and gastric cancer: evidence-based meta-analysis

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ABSTRACT – Background – Gastric cancer is the fourth most common cancer in men and the sixth among women, except for non-melanoma skin tumors, in Brazil. Epidemiological evidences reveal the multifactorial etiology of this cancer, highlighting risk factors such as: infection by the bacterium *Helicobacter pylori*, advanced age, smoking, chronic alcohol abuse, eating habits and genetic polymorphisms. Considering the context of genetic polymorphisms, there is the absence of the *GSTM1* gene. The lack of *GSTM1* function to detoxify xenobiotics and promote defense against oxidative stress leads to increased DNA damage, promoting gastric carcinogenesis. This process is multifactorial and the development of gastric cancer results from a complex interaction of these variables. **Objective –** The aim of this study was to investigate the association of *GSTM1* null polymorphism in the pathogenesis of gastric cancer. **Methods** – A meta-analysis was conducted from 70 articles collected in SciELO and PubMed databases, between September 2015 and July 2016. In order to evaluate a possible association, we used the odds ratio (OR) and confidence interval of 95% (CI 95%). To assess the heterogeneity of the studies was used the chi-square test. Statistical analysis was performed using the BioEstat® 5.3. **Results** – This study included 70 studies of case-control, including 28,549 individuals, which were assessed for the null polymorphism of the *GSTM1* gene, and of which 11,208 (39.26%) were cases and 17,341 (60.74%) were controls. The final analysis showed that the presence of the *GSTM1* gene acts as a protective factor against the development of gastric cancer (OR=0.788; 95%CI 0.725-0.857; $P<0.0001$). Positive statistical association was found in Asia (OR=0.736; 95%CI 0.670-0.809; $P<0.0001$) and Eurasia (OR=0.671; 95%CI 0.456-0.988; $P=0.05$). However, statistically significant data was not obtained in Europe (OR=1.033; 95%CI 0.873-1.222; $P=0.705$) and America (OR=0.866; 95%CI 0.549-1.364; $P=0.534$). Therefore, the results can not be deduced around the world. **Conclusion –** This meta-analysis concluded that the presence of the *GSTM1* gene is a protector for the emergence of gastric cancer, especially in Asian countries, but this result was not found in Europe and America.

HEADINGS – Stomach neoplasms. Genetic polymorphism. Meta-analysis.

INTRODUCTION

Malignant tumors of the stomach are present predominantly in the form of three histologic types: adenocarcinoma accounts for 95% of the tumors; lymphoma, diagnosed in about 3% of cases; and leiomyosarcoma, initiated in tissues that give rise to the muscles and bones[74].

In Brazil, gastric cancer is the fourth most common cancer in men and the sixth among women, except for nonmelanoma skin tumors[74]. In the rest of the world, according to the International Agency for Research on Cancer (GLOBOCAN), gastric cancer is the fourth most common cancer in men and the fifth in women[17]. More than 70% of gastric cancer cases occur in developing countries. The incidence rate of this disease is two times higher in males than in females. The peak incidence occurs mostly in men, around 70 years old. About 65% of patients diagnosed with this cancer are over 50 years old[17,74].

The highest mortality rates are recorded in Latin America, especially Costa Rica, Chile and Colombia. However, the greatest number of cases occurs in Japan, where they found 780 patients per 100,000 inhabitants. Gastric cancer does not have a good prognosis, and mortality remains high throughout the world[74].

A study conducted by the National Cancer Institute José Alencar Gomes da Silva (INCA), demonstrated that the median survival of gastric cancer after surgical resection was 15 months (0-65 months), with higher survival rates for stage I and II and lower survival for stage III and IV[11]. European data shows that only 21% of patients survive more than five years after diagnosis[7]. And therefore, in Brazil and in the world, it is a major public health problem.

The process of carcinogenesis is multifactorial and not completely understood. In addition to nutritional and behavioral factors, genetic characteristics have shown to be increasingly important. The development of gastric cancer results from a complex interaction of these variables[68,86,89]. Genetic susceptibility may modify the effect of environmental exposure, thus explaining the variations in incidence of cancer around the world[23,34].

The individuality of genetic susceptibility is critical in the various factors that influence carcinogenesis, such as: protection of the gastric mucosa in the face of infection by *Helicobacter pylori*; inflammatory response to the infection; capacity of detoxification and antioxidant protective action; cell proliferation capacity; variability in the DNA repair process; apoptotic pathway[15,49,80,92].

In addition, part of the susceptibility is determined by indi-

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vidual differences in bioactivation of proto-oncogenes and detoxification of carcinogens due to metabolism and degree of penetrance of inherited polymorphisms[34,49].

Several genes with low penetrance were identified as potential carcinogens. Glutathione S-transferase (*GST*) is a superfamily of homo- and hetero-dimeric enzymes that catalyze the conjugation of potential carcinogens in glutathione, playing an important role in protecting cell structures, including DNA[89].

In humans, eight distinct *GST* genes were found, among them five are widely distributed: alpha (*GSTA*), sigma (*GSTs*), mi (*GSTM*), pi (*GSTP*) and theta (*GSTT*)[9,49]. Located on chromosome 1p13.3, the *GSTM1* plays an important role in detoxification of xenobiotics[89]. Among the isoforms in the *GST*, the *GSTM1* has a particular function, because the null polymorphism results from the total absence of the enzyme produced by it[80].

The most common *GSTM1* polymorphism gene is a homozygous deletion (null), which has been associated with reduced enzyme activity and increased vulnerability to cytogenetic damage[89]. The *GST* enzymes commonly act on environmental pollutants, such as benzopyrene and other polycyclic aromatic hydrocarbons, which are important carcinogens. Lack of *GSTM1* function to detoxify xenobiotics and promote defense against oxidative stress leads to increased DNA damage, promoting gastric carcinogenesis[61].

The association between *GSTM1* null genotype and gastric cancer was first described by Strange in 1991 in the British population. In recent years, several studies have attempted to demonstrate a positive association between *GSTM1* null and gastric cancer. However, the results have been conflicting regarding this association[80,89].

Considering both genders, gastric cancer is the fifth most frequent cancer and third leading cause of cancer death worldwide. Proper management of this disease is a major public health problem, both nationally and internationally. Knowledge of the interactions and molecular changes involving the carcinogenic process can lead to a way for the control of gastric cancer. In this perspective, the genetic role of polymorphisms has acquired a lot of relevance in the scientific community[80]. Given this universal scenario, the aim of this study is to investigate the association of *GSTM1* null polymorphism in the genesis of gastric cancer and compare the different effects of this association in Asia, America, Europe and Eurasia.

METHODS

The meta-analysis is a research technique that selects and extracts studies results through strict procedures. The results are then summarized by statistical analysis in order to reduce the subjectivity of the traditional methods of narrative review. Thus, combining results from different primary studies and their use in recent years, added significantly to the area of health by the high degree of recommendation associated with levels of evidence that it translates[63,67].

The main steps of a meta-analysis are: (1) the literature, (2) the transformation of the results of each study group on a common measure, (3) checking the homogeneity of the results, (4) modeling variation between studies, and finally (5) the sensitivity analysis[20].

Search and retrieval studies

The research of articles was conducted from databases of Scientific Electronic Library Online (SciELO) and PubMed National Center for Biotechnology Information, USA (NCBI), between September 2015 and July 2016, for the extraction of relevant studies that estimated the association between *GSTM1* polymorphism and the risk of gastric cancer. For this, the following keywords were selected: "GSTM1", "gastric cancer", "Glutathione S-transferase M1", and "Meta-analysis". During the research, articles in Portuguese, English and Spanish were selected. Limitations were not made regarding the size of the sample obtained by surveyed items.

Inclusion and exclusion criteria

In the context of meta-analysis, it is important to assess the heterogeneity, as it consists in the variability or differences between studies in relation to the estimating effects and therefore its identification is critical to assess the degree of confidence in the results. Overall, the authors divide the heterogeneity into three types: clinical, methodological or statistical[58,73]. In order to minimize these parameters, the inclusion criteria are defined: (1) Case-control studies; (2) histologic confirmation of adenocarcinoma; (3) gene by PCR Research *GSTM1*; (4) articles published from 1990 to 2015; (5) articles in languages: English, Portuguese and Spanish; (6) articles fully accessed by researchers.

Data extraction

The extraction of relevant data were made by two researchers independently, discrepancies in data collection were discussed and a consensus was reached among researchers. Data taken from the table were: year of publication of the article, lead author, country, continent, number of cases and controls and presence of polymorphisms of *GSTM1* in cases and controls.

Statistical analysis

Heterogeneity is defined as the diversity of the studies and can strongly affect the results. The diversity can then be evaluated for heterogeneity χ^2 test[58,73]. Thus, the genotypic frequencies of all articles were grouped into a single table and diversity was assessed with the use of heterogeneous χ^2 test in 2x2 contingency tables, to compare the different odds ratios (OR) with a confidence interval of 95%, determined in their studies.

If the heterogeneity of the χ^2 test reveals a $P>0.05$, the null hypothesis is confirmed, i.e., the studies are homogeneous. So it is recommended to use the fixed-effect tests that assume that all studies point in the same direction. In this context, the most used is the Mantel-Haenszel test. On the other hand, if the heterogeneity χ^2 test results in a $P<0.05$, it indicates diversity and heterogeneity between studies. Therefore, the use of random or random effect tests is recommended, such as the DerSimonian-Laird tests[4,6,26,91].

Global association tests were then used to assess the significance of the correlation between the polymorphism of gene *GSTM1* and gastric cancer for all studies combined. To estimate the effect of gene polymorphism in the development of gastric cancer, the amounts of each study were combined with fixed and random tests of effects utilizing the software BioEstat® 5.3[26]. Either for fixed-effect tests or for the random effects, odds ratios are calculated, its confidence intervals (95%) and the weights for each individual and combined study, generating an estimated combined effect. In addition, the tests elaborate a graphical *forest plot* type. The advantage of these charts is to summarize, in the same space, all the information on the effect and the contribution of each study for analysis[73].

As the grouping of all studies showed heterogeneity, we applied the random effects test DerSimonian-Laird for all genotypic

possibilities: the presence or absence of the *GSTM1*. This same grouping strategy was used to stratify studies by more frequent locations: Asia (50 studies), Europe (12 studies), America (5 studies) and Eurasia (3 studies). For groupings with the presence of gastric cancer realized in Asia, America and Europe, they utilized the DerSimonian-Laird test. On the other hand, for the variables of the locations in Eurasia, the fixed effect Mantel-Haenszel test was applied.

RESULTS

In this meta-analysis, after researching databases, we selected 174 articles on the polymorphism of the *GSTM1* gene, published between the years 1991 to 2015. Of these articles, 104 articles were discarded for not meeting the inclusion criteria (Figure 1). Thus, 70 articles were brought together that evaluated the association of *GSTM1* polymorphism and gastric cancer.

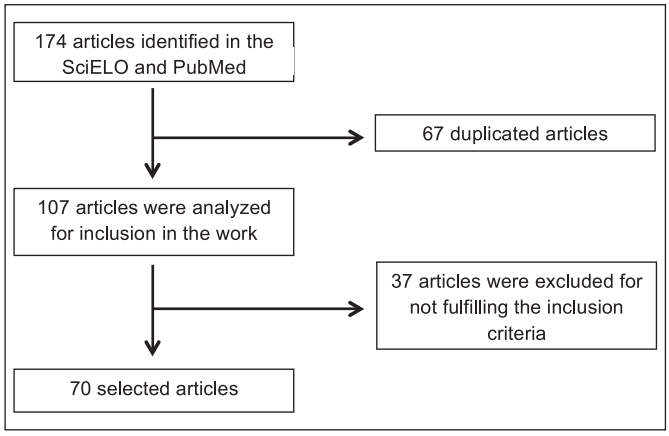

FIGURE 1. Identification of criteria, inclusion and exclusion, of the meta-analysis studies.

Among the articles selected, 50 were made in Asia, 12 in Europe, 5 in the Americas (North, Central and South) and 3 in Eurasia. This study included 28,549 individuals assessed for polymorphism of the *GSTM1* gene, of which 11,208 (39.26%) were part of the group of cases diagnosed with gastric cancer, and 17,341 (60.74%) were part of the control group. For comparison purposes, to group the data, the frequency of the presence of the *GSTM1* gene in cases and controls were, respectively, 46.0% and 50.4%.

The data of the *GSTM1* polymorphism of the gene were grouped into each article. Thus, the odds ratios (OR) were calculated for each study, their variations within the 95% confidence interval and significance probabilities (*P*).

For each cluster, we applied the DerSimonian-Laird test, except for the grouping in Eurasia, where we used the Mantel-Haenszel. The odds ratios were calculated with the grouping of all studies for: America (OR=0.866; 95%CI 0.549-1.364; *P*=0.534; Figure 2), Eurasia (OR=0.671; 95%CI 0.456-0.988; *P*=0.05; Figure 3), Europe (OR=1.033; 95%CI 0.873-1.222; *P*=0.705; Figure 4) and Asia (OR=0.736; 95%CI 0.670-0.809; *P*<0.0001).

The graphics generated in the meta-analysis are the *forest plot* type. This type of chart, each line represents one study, with the latter, in the shape of a rhombus, represents the combined results. The result of each study is described in graphical and numerical forms. In graphic form, the central squares represent the relative risk

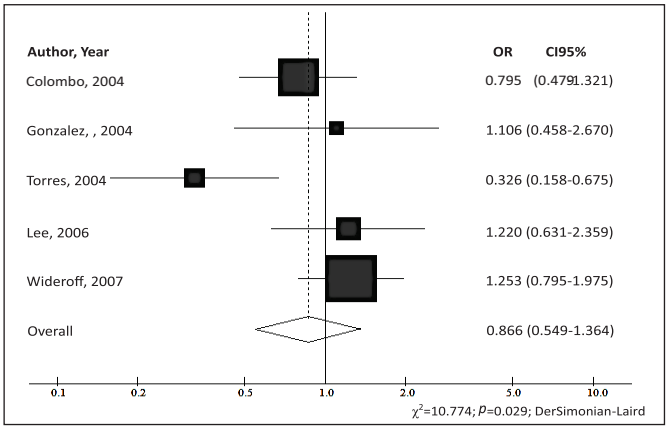

FIGURE 2. Odds ratios (OR) and confidence interval of 95% (95%CI) of the association between gastric cancer and the presence of *GSTM1* for the studies carried out in America with the Chi-square test of significant heterogeneity (DerSimonian-Laird test).

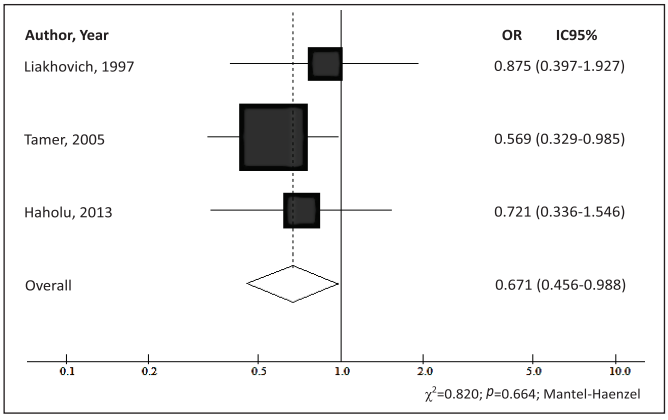

FIGURE 3. Odds ratios (OR) and confidence interval of 95% (95%CI) of the association between gastric cancer and the presence of *GSTM1* for the studies carried out in Eurásia with the Chi-square test of significant heterogeneity (Mantel-Haenzel test).

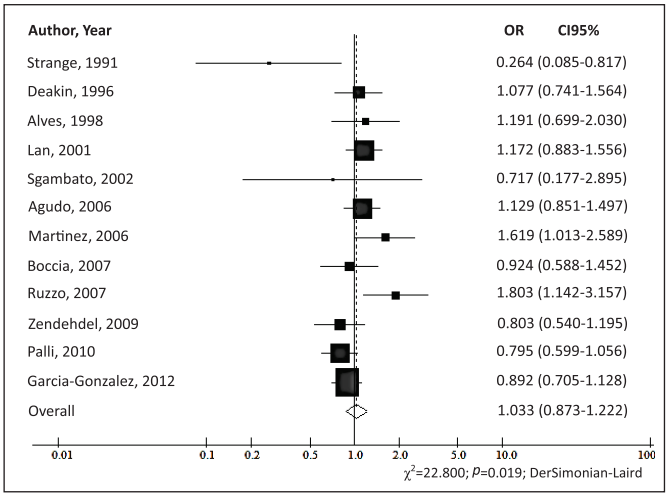

FIGURE 4. Odds ratios (OR) and confidence interval of 95% (95%CI) of the association between gastric cancer and the presence of *GSTM1* for the studies carried out in Europa with the Chi-square test of significant heterogeneity (DerSimonian-Laird test).

(RR) or odds ratio and the traits represent the confidence intervals (CI). When the CI does not exceed the null line (position 1.0 in the chart), it can be said that the study is statistically significant, both individually and for the combined value. The larger the sample group considered in the study, narrower will be the CIs and greater will be the area of the square, showing more accurate results and greater contribution to the meta-analysis.

Additionally, information on the polymorphism of gene *GSTM1* were grouped into each article, we calculated the OR, the variation of OR within the 95% confidence interval and the probability of significance (*P*) (Table 1). When applying DerSimonian-Laird test, the OR of all the combined work (OR=0.788; 95%CI 0.725-0.857; *P*<0.0001) showed that the presence of the gene is a protective factor for gastric cancer.

TABLE 1. Distribution of the polymorphism of the *GSTM1* gene in patients with gastric cancer, in the case and control groups in the published articles between 1991 and 2015 and the database of the current study

Author	Year	Case				Control				OR	CI (95%)		Weight
		GSTM1 (+)		*GSTM1* (-)		*GSTM1* (+)		*GSTM1* (-)			Inf.	Sup.	
		n	F (%)	n	F (%)	n	F (%)	n	F (%)				
Strange[75]	1991	5	26.3	14	73.7	29	59.2	20	40.8	0.264	0.085	0.817	2.999
Harada[25]	1992	5	26.3	14	73.7	44	52.4	40	47.6	0.175	0.057	0.531	3.105
Kato[31]	1996	34	53.1	30	46.9	59	49.2	61	50.8	1.169	0.639	2.128	10.544
Katoh[32]	1996	60	43.2	79	56.8	71	56.3	55	43.7	0.591	0.364	0.959	16.364
Deakin[14]	1996	64	47.1	72	52.9	261	45.2	316	54.8	1.077	0.741	1.564	27.563
Liakhovich[42]	1997	28	57.1	21	42.9	32	60.4	21	39.6	0.877	0.401	1.915	6.294
Ng[54]	1998	23	45.1	28	54.9	22	62.9	13	37.1	0.495	0.208	1.179	5.098
Wang[81]	1998	34	41.0	49	59.0	43	51.8	40	48.2	0.649	0.353	1.194	10.323
Alves[3]	1998	77	52.0	71	48.0	40	47.6	44	52.4	1.191	0.699	2.030	13.504
Oda[56]	1999	56	38.1	91	61.9	57	50.9	55	49.1	0.596	0.363	0.979	15.616
Jiang[29]	2000	17	41.5	24	58.5	27	65.9	14	34.1	0.377	0.156	0.911	4.919
Liu[43]	2000	36	36.4	63	63.6	178	48.9	186	51.1	0.601	0.381	0.941	18.481
Cai[8]	2001	35	36.8	60	63.2	51	54.3	43	45.7	0.496	0.278	0.884	11.481
Qian[60]	2001	34	38.2	55	61.8	50	53.2	44	46.8	0.548	0.305	0.984	11.201
Shen[70]	2001	67	55.4	54	44.6	80	66.1	41	33.9	0.638	0.381	1.071	14.351
Saadat[66]	2001	16	38.1	26	61.9	78	59.5	53	40.5	0.424	0.209	0.860	7.706
Setiawan[68]	2001	45	51.7	42	48.3	207	49.4	212	50.6	1.096	0.692	1.736	18.171
Lan[38]	2001	180	51.9	167	48.1	204	47.9	222	52.1	1.172	0.883	1.556	47.859
Wu[84]	2002	183	51.4	173	48.6	142	51.1	136	48.9	1.013	0.741	1.386	39.128
Gao[18]	2002	63	41.2	90	58.8	90	40.4	133	59.6	1.035	0.682	1.571	22.056
Gong[21]	2002	7	21.9	25	78.1	38	43.2	50	56.8	0.386	0.154	0.964	4.580
Zheng[94]	2002	28	30.4	64	69.6	44	47.8	48	52.2	0.482	0.264	0.877	10.674
Sgambato[69]	2002	3	37.5	5	62.5	47	47.0	53	53.0	0.717	0.177	2.895	1.971
Choi[10]	2003	34	42.5	46	57.5	82	46.3	95	53.7	0.859	0.506	1.459	13.683
Zhang[90]	2003	49	38.6	78	61.4	61	53.5	53	46.5	0.549	0.329	0.914	14.729
Zheng[93]	2003	168	53.7	145	46.3	106	55.2	86	44.8	0.941	0.656	1.348	29.623
Zhou[95]	2003	12	63.2	7	36.8	44	61.1	28	38.9	1.067	0.385	2.961	3.691
Colombo[12]	2004	53	53.0	47	47.0	88	58.7	62	41.3	0.795	0.479	1.321	14.916
Gonzalez[22]	2004	16	51.6	15	48.4	25	49.0	26	51.0	1.106	0.458	2.670	4.949
Torres[78]	2004	16	34.8	30	65.2	60	62.5	36	37.5	0.326	0.158	0.675	7.282
Roth[64]	2004	66	73.3	24	26.7	309	68.1	145	31.9	1.276	0.771	2.111	15.161
Suzuki[76]	2004	58	40.0	87	60.0	93	52.5	84	47.5	0.604	0.388	0.941	19.588
Shen[72]	2004	29	48.3	31	51.7	36	60.0	24	40.0	0.629	0.307	1.288	7.471
Shen[71]	2005	71	50.0	71	50.0	314	46.5	361	53.5	1.149	0.801	1.649	29.483
Lai[37]	2005	50	40.7	73	59.3	66	54.5	55	45.5	0.573	0.346	0.950	15.046
Li[41]	2005	33	33.0	67	67.0	36	58.1	26	41.9	0.360	0.188	0.690	9.108
Mu[51]	2005	69	35.2	127	64.8	158	40.2	235	59.8	0.810	0.568	1.155	30.500
Nan[52]	2005	149	37.3	251	62.8	254	41.4	360	58.6	0.842	0.650	1.090	57.576
Nan[53]	2005	34	31.8	73	68.2	90	40.9	130	59.1	0.677	0.417	1.100	16.312
Tamer[77]	2005	30	42.9	40	57.1	116	56.9	88	43.1	0.572	0.332	0.987	12.926
Lee[40]	2006	60	82.2	13	17.8	207	78.7	56	21.3	1.220	0.631	2.359	8.840
Hong[27]	2006	48	44.4	60	55.6	104	43.7	134	56.3	1.320	0.654	1.628	18.467
Zhou[96]	2006	33	33.0	67	67.0	36	58.1	26	41.9	0.360	0.188	0.690	9.108
Agudo[1]	2006	120	49.6	122	50.4	434	46.6	498	53.4	1.129	0.851	1.497	48.147
Martinez[47]	2006	65	66.3	33	33.7	180	54.7	149	45.3	1.619	1.013	2.589	17.438
Wideroff[83]	2007	55	47.4	61	52.6	87	41.8	121	58.2	1.253	0.795	1.975	18.540
Tripathi[79]	2007	45	59.2	31	40.8	61	61.0	39	39.0	0.928	0.507	1.699	10.493
Boccia[5]	2007	48	44.9	59	55.1	119	46.9	135	53.1	0.924	0.588	1.452	18.806
Ruzzo[65]	2007	91	72.2	35	27.8	83	57.6	61	42.4	1.898	1.142	3.157	14.851
Al-Moundhri[2]	2009	65	60.7	42	39.3	75	70.1	32	29.9	0.663	0.377	1.166	12.076
Masoudi[48]	2009	30	44.8	37	55.2	74	55.2	60	44.8	0.660	0.368	1.187	11.185
Malik[46]	2009	44	40.7	64	59.3	116	59.5	79	40.5	0.471	0.292	0.758	16.910
Moy[50]	2009	72	42.4	98	57.6	320	43.5	415	56.5	0.954	0.682	1.336	33.930
Piao[59]	2009	988	44.6	1225	55.4	776	45.7	923	54.3	0.959	0.845	1.089	238.192
Huang[28]	2009	55	45.5	66	54.5	84	60.9	54	39.1	0.538	0.329	0.881	15.813
Zendehdel[87]	2009	54	43.5	70	56.5	230	49.0	239	51.0	0.803	0.540	1.195	24.362
Nguyen[55]	2010	16	27.1	43	72.9	34	31.2	75	68.8	0.830	0.414	1.664	7.948
Yadav[85]	2010	84	63.2	49	36.8	150	55.6	120	44.4	1.367	0.894	2.090	21.286
Palli[57]	2010	130	43.9	166	56.1	271	49.6	275	50.4	0.795	0.599	1.056	47.660
Darazy[13]	2011	7	53.8	6	46.2	58	82.9	12	17.1	0.247	0.073	0.831	2.602
Luo[44]	2011	30	24.4	93	75.6	58	45.0	71	55.0	0.399	0.233	0.610	13.412
Zhang[88]	2011	89	45.9	105	54.1	218	52.9	194	47.1	0.755	0.534	1.063	32.927
Yadav[86]	2011	30	73.2	11	26.8	92	70.8	38	29.2	1.104	0.508	2.397	6.389
Jing[30]	2012	170	41.5	240	58.5	203	49.5	207	50.5	0.723	0.549	0.952	50.617
Malakar[45]	2012	45	44.1	57	55.9	107	52.5	97	47.5	0.718	0.446	1.155	16.970
Wang[82]	2012	90	69.8	39	30.2	112	81.2	26	18.8	0.540	0.307	0.949	12.050
Kim[33]	2012	41	40.2	61	59.8	76	38.0	124	62.0	1.098	0.676	1.785	16.271
Garcia-Gonzalez[19]	2012	274	49.2	283	50.8	290	52.1	267	47.9	0.892	0.705	1.128	69.682
Eom[16]	2013	214	44.9	263	55.1	217	45.6	259	54.4	0.971	0.753	1.253	59.142
Haholu[24]	2013	24	48.0	26	52.0	32	56.1	25	43.9	0.725	0.341	1.554	6.732
Total		5154	46.0	6054	54.0	**8736**	**50.4**	**8605**	**49.6**	**0.788**	**0.725**	**0.857**	***P*<0.0001**

The heterogeneity chi-square test was used in 2x2 tables of all the possibilities: Asia (χ^2=99,489; DF=49; *P*<0.0001); Europe (χ^2=22.800; DF=11, *P*=0.019); America (χ^2=10.774; DF=4; *P*=0.029); Eurasia (χ^2=0.820; DF=2, *P*=0.664); and finally, gathering all studies (χ^2=154,651; DF=69; *P*<0.0001). Thus, tests have revealed significant (*P*<0.05) with the American, Asian and European groupings, indicating that there is a difference between them only as a result of sampling error, i.e., the real effect is the same in each of the studies. However, in the Eurasia group, the test is found to be significant (*P*>0.05). However, data from all articles analyzed points to the same statistical direction (*P*<0.0001), then it is concluded that when all the samples are grouped, the articles are homogeneous and differences can be seen as resulting from random or common effects.

Table 2 shows an overview of all groups, with their heterogeneity χ^2 tests, indicating the *P*-value, which determines the type of test used in the meta-analysis. Verification tests of the correlation of the *GSTM1* gene polymorphism with gastric cancer, in various grouping situations, were sometimes random effects of DerSimonian-Laird, and at other times of fixed effect Mantel-Haenszel. It can be observed in Table 2 that the *p* values, in the meta-analysis, revealed no association between the variables studied (*P*>0.05) in Europe and America, and for the grouping of studies in Asia and Eurasia could be inferred that there is a positive association (Asia, *P*<0.0001 and Eurasia, *P*=0.05).

The data in Table 2 indicates that the meta-analysis of 70 case-control studies investigating the association between polymorphisms of *GSTM1* and the risk of developing gastric cancer was positively correlated, and therefore the presence of the gene a protective factor. Regarding the groupings performed, there is a positive correlation in the group of Asian and Eurasian studies, but no correlation was observed in studies conducted in Europe and America.

DISCUSSION

The pathogenesis of gastric cancer is not yet fully known. In recent years, it was understood that the knowledge that the process of developing this cancer is multifactorial, in which the environment and genetic susceptibility factors are decisive[35].

Among the biological factors, infection by the bacterium *Helicobacter pylori* plays an important correlation with gastric cancer due to their role in chronic atrophic gastritis, since gastric carcinoma is accompanied by hypochlorhydria in 85% to 90% of cases[39].

The *H. pylori* infection still remains the greatest risk factor for the development of gastric cancer, increasing the incidence of this cancer about six times. It is one of the most common infections of the population, with a worldwide prevalence estimated at between 50% and 90% in developing countries. However, it is important to mention that, in populations with a high prevalence of infection by *H. pylori*, a small fraction of infected develop gastric cancer[74].

The risk of intestinal metaplasia in the gastric antrum depends largely on the presence of a peptic ulcer and other factors, such as individual variability of the immune response, advanced age, smoking, chronic alcohol abuse, and eating habits. Therefore, additional factors alter the relationship of *H. pylori* to gastric carcinogenesis[61]. Chen and colleagues showed that risk factors such as smoking and *Helicobacter pylori* infection did not modify the association between *GSTM1* null and risk for gastric cancer, suggesting greater genetic influence in the etiology of this cancer[9].

Significant associations of the absence of the *GSTM1* gene and the incidence of gastric cancer were found in Asians, but it was not possible to demonstrate such an outcome in Caucasian and African populations, suggesting a possible influence of ethnic differences, genetic origins and the environment. The influence of *GSTM1* null allele can be masked by the presence of other causative genes, not yet identified, involved in the development of gastric cancer in Caucasians and Africans[34,61,97].

According to Rebbeck and colleagues, ethnic differences were found related to the prevalence of *GSTM1* deletion gene in different populations. In Japanese, this frequency varies between 48% to 51% of the population, in Chinese between 35% to 65%, in Indians 33% to 36%, 50% in Caucasians and Africans 22% to 35%[62].

Another risk factor that already has well-established relationship in the genesis of gastric cancer is smoking. It is estimated that smoking increases the risk of this cancer by 50%. A meta-analysis conducted in 2008 by Ladeiras-Lopes and colleagues estimated that smoking is the main modifiable risk factor related to gastric cancer, especially in men[36].

Tobacco is composed of more than 4,000 different compounds, 50 proven carcinogens. Pollutants such as benzopyrene and other polycyclic aromatic hydrocarbons are substrates of enzymes of the GST family and have serious carcinogenic activity. These compounds are primarily metabolized by Phase I enzymes, detoxified and converted into inactive metabolites by enzymes of Phase II, enzymes expressed by the gene *GSTM1*[39].

The null genotype refers to the complete absence of enzyme activity *GSTM1*, and can thus increase the risk of gastric cancer. The lack of function of this gene leads to the accumulation of toxic intermediate, resulting in greater damage to DNA, which facilitates carcinogenesis[25,36,61].

TABLE 2. Summary of the groupings, showing the chi-square test of heterogeneity and the type of the test realized in the meta-analysis.

Parameters	Number of studies	Heterogeneity			Meta-analysis				
		χ^2	gl	*P*-value	Test	OR	CI (95%)	CI (95%)	*P*-value
Geral									
GSTM1 (+) x *GSTM1* (-)	70	154.651	69	<0.0001	DSL	0.788	0.725	0.857	<0.0001
Region									
America	5	10.774	4	0.0292	DSL	0.866	0.549	1.364	0.534
Asia	50	99.489	49	<0.0001	DSL	0.736	0.670	0.809	<0.0001
Eurasia	3	0.820	2	0.6637	MH	0.671	0.456	0.988	0.050
Europe	12	22.800	11	0.0189	DSL	1.033	0.873	1.222	0.705

DSL: DerSimonian–Laird; MH: Mantel–Haenszel.

CONCLUSION

The meta-analysis included 70 articles published between 1991 and 2015. The group generated a simultaneous universal evaluation of the *GSTM1* null polymorphism in 28,549 individuals, 11,208 patients with gastric cancer and 17,341 controls.

The current study showed that there is a significant positive association between *GSTM1* null genotype and gastric cancer, with $P<0.0001$. The presence of *GSTM1* gene is protective in cases of gastric cancer (OR=0.788).

Prior studies of this association are quite controversial. The work carried out in Asia are those that showed strong correlation between variables ($P<0.001$); on the other hand, as reported in previous references, the data collected in Europe ($P=0.705$) and the Americas ($P=0.534$) did not find such an association. It is important to note the composition of this meta-analysis, the Asian articles contributed 20,257 individuals, 8,465 cases and 11,792 controls. The Americas articles contributed 1,134 individuals (366 cases and 768 controls) and European data with 6,675 individuals (2,208 cases and 4,467 controls).

The process of carcinogenesis is multifactorial and not fully understood. Genetic susceptibility may modify the effect of environmental exposure, thus explaining the variations in the incidence of gastric cancer around the world and the results found in this meta-analysis: positive relationship between *GSTM1* null and gastric cancer, especially when considering Asian countries.

Future studies with larger range of individuals are needed to better understand the association between *GSTM1* null and gastric cancer, especially in the continents in which such an association were not found, such as Europe and the Americas.

Authors' contributions

Ribeiro RX: performed research, drafted the research project, took data collection, wrote the preliminary versions of the article. Nascimento CILL: performed research, drafted the research project, took data collection, wrote the preliminary versions of the article. Silva AMTC: oriented study at all stages of execution, did the study statistics and edited the preliminary versions of the article, generating the final version.

Ribeiro RX, Nascimento CILL, Silva AMTC. Associação do genótipo nulo *GSTM1* e o câncer gástrico: evidências baseadas em meta-análise. Arq Gastroenterol. 2017;54(2):101-8.

RESUMO – Contexto – No Brasil, o câncer gástrico é o quarto mais comum em homens e o sexto entre as mulheres, excetuando-se os tumores de pele não melanoma. Aspectos epidemiológicos evidenciam a etiologia multifatorial desta neoplasia, destacando como fatores de risco: a infecção pela bactéria *Helicobacter pylori*, idade avançada, tabagismo, etilismo crônico, hábitos alimentares e polimorfismos genéticos. No contexto dos polimorfismos genéticos, tem-se a ausência do gene *GSTM1*. A falta da função de *GSTM1* em detoxificar xenobióticos e promover defesa contra o estresse oxidativo, leva ao maior dano do DNA, favorecendo a carcinogênese gástrica. Este processo é multifatorial e o desenvolvimento do câncer gástrico resulta de uma interação complexa dessas variáveis. **Objetivo** – O objetivo do presente estudo foi investigar a associação do polimorfismo nulo de *GSTM1* na gênese do câncer gástrico. **Métodos** – Foi conduzida uma meta-análise a partir de 70 artigos colhidos dos bancos de dados: SciELO e PubMed, entre setembro de 2015 e julho de 2016. Para avaliar uma possível associação, utilizou-se o *odds ratio* (OR) e intervalo de confiança de 95% (IC 95%). Para avaliar a heterogeneidade dos estudos, utilizou-se o teste do qui-quadrado. A análise estatística foi realizada utilizando-se o BioEstat® 5.3. **Resultados –** A presente pesquisa contou com 70 estudos do tipo caso-controle que incluíram 28.549 indivíduos avaliados para o polimorfismo nulo do gene *GSTM1*, dos quais 11.208 (39,26%) eram casos e 17.341 (60,74%) eram controles. A análise final mostra que a presença do gene *GSTM1* funciona como um fator de proteção contra o desenvolvimento de câncer gástrico (OR=0,788; IC95% 0,725-0,857; $P<0,0001$). Associação estatística positiva foi encontrada na Ásia (OR=0,736; IC95% 0,670-0,809; $P<0,0001$) e Eurásia (OR=0,671; IC95% 0,456-0,988; $P=0,05$). No entanto, não temos dados com significância estatística da Europa (OR=1,033; IC95% 0,873-1,222; $P=0,705$) e América (OR=0,866; IC95% 0,549-1,364; $P=0,534$) para inferir proteção ao câncer gástrico no mundo. **Conclusão** – Esta meta-análise, conclui que a presença do gene *GSTM1* é protetora para o surgimento do câncer gástrico, principalmente nos países asiáticos, porém tal resultado não foi encontrado se comparado isoladamente os estudos realizados na Europa e na América.

DESCRITORES – Neoplasias gástricas. Polimorfismo genético. Meta-análise.

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