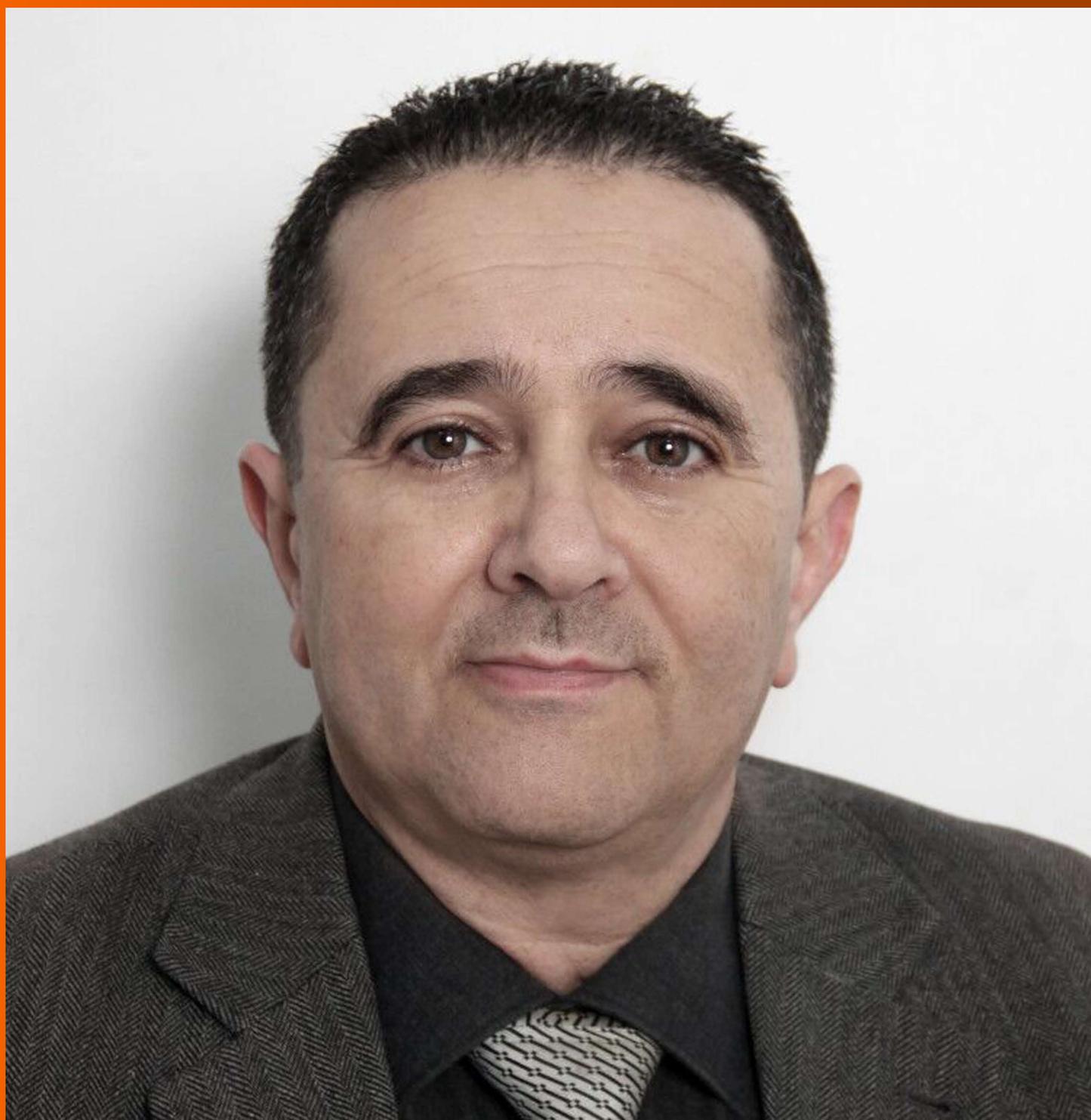


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Case Control Study

Molecular evaluation of glutathione S transferase family genes in patients with sporadic colorectal cancer

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Abstract**AIM**

To evaluate the association between polymorphisms

in glutathione S transferases (GSTs) and the risk of sporadic colorectal cancer (SCRC), tumor progression and the survival of patients.

METHODS

A case-control study of 970 individuals from the Brazilian population was conducted (232 individuals from the case group with colorectal cancer and 738 individuals from the control group without a history of cancer). PCR multiplex and PCR-RFLP techniques were used to genotype the GST polymorphisms. The tumors were categorized according to the TNM classification: tumor extension (T), affected lymph nodes (N), and presence of metastasis (M). Logistic regression, multiple logistic regression and survival analysis were used to analyze the data. The results are presented in terms of odds ratio (OR) and 95% confidence interval (CI). The level of significance was set at 5% ($P \leq 0.05$).

RESULTS

Age equal to or over 62 years (OR = 8.79; 95%CI: 5.90-13.09, $P < 0.01$) and female gender (OR = 2.91; 95%CI: 1.74-4.37; $P < 0.01$) were associated with increased risk of SCRC. Analysis of the polymorphisms revealed an association between the *GSTM1* polymorphisms and a risk of SCRC (OR = 1.45; 95%CI: 1.06-2.00; $P = 0.02$), as well as between *GSTT1* and a reduced risk of the disease (OR = 0.65; 95%CI: 0.43-0.98; $P = 0.04$). An interaction between the presence of the wild-type allele of *GSTP1* Ile105Val polymorphism and tobacco consumption on risk of SCRC (OR = 2.33; 95%CI: 1.34-4.05; $P = 0.05$) was observed. There was an association between the *GSTM1* null genotype and the presence of advanced tumors (OR = 2.33; 95%CI: 1.23-4.41; $P = 0.009$), as well as increased risk of SCRC in the presence of a combination of *GSTT1* non-null/*GSTM1* null genotypes (OR = 1.50; 95%CI: 1.03-2.19; $P = 0.03$) and *GSTT1* non-null/*GSTM1* null/*GSTP1* Val* (OR = 1.85; 95%CI: 1.01-3.36, $P = 0.04$). Combined *GSTT1* non-null/*GSTM1* null genotypes (OR = 2.40; 95%CI: 1.19-4.85; $P = 0.01$) and *GSTT1* non-null/*GSTM1* null/*GSTP1* Val* (OR = 2.92; 95%CI: 1.05-8.12; $P = 0.04$) were associated with tumor progression. Polymorphisms were not associated with the survival of patients with SCRC.

CONCLUSION

Females aged 62 years or older are more susceptible to SCRC. Polymorphisms of *GSTT1* and *GSTM1* null genotypes modulated the susceptibility to SCRC in the population studied.

Key words: Colorectal neoplasms; Smoking; Alcohol; Glutathione S transferase; Genetic polymorphisms

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Core tip: Sporadic colorectal cancer (SCRC) is the third most common cancer worldwide and includes malignancies that occur in the colon and rectum. Age

greater than 60 years, smoking, and alcohol habits are some of the risk factors for SCRC. Detoxification and elimination of carcinogens contained in tobacco and alcohol require metabolic activation mediated by enzymes that metabolize the xenobiotics (XME). Polymorphisms in genes such as *GSTP1*, *GSTT1*, and *GSTM1* that encode enzymes involved in XMEs may be related to important processes in colorectal carcinogenesis.

Rodrigues-Fleming GH, Fernandes GMM, Russo A, Biselli-Chicote PM, Netinho JG, Pavarino ÉC, Goloni-Bertollo EM. Molecular evaluation of glutathione S transferase family genes in patients with sporadic colorectal cancer. *World J Gastroenterol* 2018; 24(39): 4462-4471 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i39/4462.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i39.4462>

INTRODUCTION

Colorectal cancer is the third most frequent cancer worldwide^[1] and the fifth most frequent type of cancer in Brazil^[2]. Estimates for the year 2018 in Brazil are 17380 new cases for men and 18980 new cases for women^[2].

Sporadic colorectal cancer (SCRC) develops from polyps (adenomas) in the colon and rectum walls, of varying sizes, and can change to dysplasia, triggering the development of cancer^[2-4].

SCRC is a multifactorial disease, influenced by genetic factors, such as mutations or polymorphisms in genes that participate in pathways responsible for regulating cell growth, including tumor suppressor genes and proto-oncogenes^[5,6]. Other related factors are age, gender, environmental factors, and lifestyle habits such as smoking and alcohol consumption^[7]. Genetic factors may influence the effect of the environment on predisposition to the disease. Therefore, the incidence of SCRC varies among populations^[1,8,9].

There are many genes encoding enzymes responsible for the metabolism of xenobiotics, in which detoxification occurs. Some of the major genes involved in phase II are the cytosolic glutathione S transferase (GST) superfamily, including GST mi (*GSTM1*), theta (*GSTT1*), and pi (*GSTP1*)^[10,11]. These catalyze the conjugation of structurally different by-products of oxidative stress and xenobiotics to glutathione (GSH), which leads to the elimination of toxic substances from the cells and the protection of important cellular components such as nucleic acids and proteins^[12]. GST gene expression varies between different tissues and cell types^[13].

In addition to being very common in the general population, the complete absence of *GSTT1* and/or *GSTM1* may alter their expression or the activity of the protein itself^[14]. In general, *GSTP1* appears to be highly expressed in proliferating cells compared with differentiated cells. In addition, many of the GSTs are overexpressed in various neoplastic cells and higher

levels are observed in aggressive cancer cells^[15]. The change in the *GSTP1* gene also significantly alters the enzymatic activity^[16,17], influencing the detoxification of carcinogens, causing DNA damage, and exerting an indirect effect on the risk of cancer development^[18].

Therefore, the objectives of this study were to evaluate the association of epidemiological risk factors and these polymorphisms with the development of SCRC, the interaction between these polymorphisms and both smoking and alcohol habits, and the association between the polymorphisms and clinical-histopathological parameters and survival among patients with SCRC.

MATERIALS AND METHODS

Approval and consent

The study was approved by the Ethics Committee-Medical School of Sao Jose do Rio Preto - FAMERP (No. 012/2012). The 970 individuals who agreed to participate in the study signed a consent form. The variables analyzed included gender, age, ethnicity, profession, smoking, alcohol consumption, and personal and familial history of cancer.

Study populations

The case group consisted of 232 (112 men and 120 women) patients from the Department of Coloproctology of the Base Hospital of Sao Jose do Rio Preto who received the clinical and/or histopathological diagnosis of SCRC between 2010 and 2016. The exclusion criterion was previous treatment with chemotherapy and/or radiotherapy. The control group included 738 (370 men and 368 women) blood donors from the Blood Center of Sao Jose do Rio Preto. The exclusion criterion for controls was personal and family history of cancer in at least three previous generations. Individuals who had smoked at least 100 cigarettes throughout their lives were considered smokers, and those who drank more than four servings of alcohol per week (one serving corresponded to 30 mL of liquor, a 102-mL glass of wine containing 12% alcohol, or a 340-mL can of beer) were considered alcohol consumers^[19,20]. SCRC was categorized according to TNM classification: tumor extension (T), affected lymph nodes (N), and presence of metastasis (M)^[21].

Molecular analysis

Analysis of the *GSTT1* and *GSTM1* polymorphisms was performed using the polymerase chain reaction (PCR) multiplex technique, with the *CYP1A1* gene as the internal positive control of amplification^[22]. PCR products were analyzed on 1.5% agarose gel stained with red gel.

Analysis of the *GSTP1* A313G polymorphism was performed using the polymerase chain reaction-polymorphism restriction fragment chain reaction (PCR-RFLP) technique with primers described by Harries *et al.*^[23]. The 176 base pair (bp) PCR products were analyzed by electrophoresis in 1.5% agarose gel stained

with red gel. The restriction enzyme digestion was performed using *Bsm*I. The results and genotyping were performed after 2.0% agarose gel electrophoresis stained with red gel. The presence of 91 and 85 bp bands corresponded to the GG polymorphic genotype; the 176, 91, and 85 bp bands corresponded to the heterozygous genotype AG; and the 176 bp band corresponded to the wild-type AA genotype.

Statistical analysis

Descriptive statistics included mean values, standard deviation for continuous data, and percentage for categorical data. The Hardy-Weinberg equilibrium (HWE) was evaluated using the chi-square test through the BioEstat Program version 5.0. The binary logistic regression model, using the Minitab/Windows-Version 12.22 program, was used to evaluate the association of age, gender, smoking, and drinking habits with SCRC, and to evaluate the association between SCRC and clinical-histopathological parameters. Binary multiple logistic regression, adjusted for age, gender, and smoking and drinking habits, was used to evaluate the association between the genetic models of the polymorphisms and the development of SCRC using the SNPStats program (available at: http://bioinfo.iconcologia.net/SNPstats_web). The effect of the polymorphisms was evaluated in the models as (1) codominant (heterozygous vs wild-type homozygous and polymorphic homozygous vs wild-type homozygous); (2) dominant (heterozygous + polymorphic homozygous vs wild-type homozygous); (3) recessive (homozygous polymorphic vs wild-type homozygous + heterozygous); (4) overdominant (heterozygous vs wild-type homozygous + polymorphic homozygous); or (5) additive (polymorphic homozygous with 2 + heterozygous vs wild-type homozygous). The SNPStats program was used to evaluate the interaction between the polymorphisms and smoking habit, adjusted for age, gender, and alcohol consumption, and to evaluate the interaction between polymorphisms and alcohol consumption, adjusted for age, gender, and smoking, in SCRC risk. The effect of the polymorphisms on the overall survival time of SCRC patients was analyzed by the Kaplan-Meier curve and log rank test using the StatsDirect version 2.7.2 program. The results are presented in terms of odds ratio (OR) and 95% confidence interval (CI). For all statistical analyses the level of significance was set at 5% ($P < 0.05$).

RESULTS

Sociodemographic data

Table 1 presents the demographic data of SCRC patients and controls. Age equal to or above 62 years (OR = 8.79; 95%CI: 5.90-13.09; $P < 0.01$) and female gender (OR = 2.91; 95%CI: 1.74-4.37; $P < 0.01$) were associated with a risk of SCRC. The genotypic frequencies of *GSTP1* Ile105Val polymorphism were observed in the HWE in both groups (Case: $P = 1$, Control: $P = 0.29$).

Table 1 Sociodemographic characteristics, risk factors, and polymorphisms *GSTT1*, *GSTM1*, *GSTP1* A313G in patients with colorectal cancer and controls *n* (%)

Variables		Case (<i>n</i> = 232)	Control (<i>n</i> = 738)	OR ¹ (95%CI)
Gender				
Male		112 (48)	370 (50)	1.00
Female		120 (52)	368 (50)	2.91 (1.94-4.37) ^a
Age [yr (mean) ± SD]		(62) ± 12	(48) ± 12	
< 62		112 (49)	621 (84)	1.00
≥ 62		120 (51)	117 (16)	8.79 (5.90-13.09) ^a
Smoking Habit				
Non-smoker		130 (56)	465 (63)	1.00
Smoker		102 (44)	273 (37)	1.45 (0.98-2.14)
Alcohol Consumption				
Non-drinker		132 (57)	395 (54)	1.00
Drinker		100 (43)	343 (46)	1.28 (0.85-1.91)
<i>GSTP1</i>				
Codominant	A/A	227 (43.7)	107 (46.1)	1.00
	A/G	224 (43.2)	102 (44)	1.06 (0.73-1.54)
	G/G	68 (13.1)	23 (9.9)	0.88 (0.48-1.59)
Dominant	A/A	227 (43.7)	107 (46.1)	1.00
	A/G-G/G	292 (56.3)	125 (53.9)	1.02 (0.71-1.45)
Recessive	A/A-A/G	451 (86.9)	209 (90.1)	1
	G/G	68 (13.1)	23 (9.9)	0.85 (0.48-1.50)
Overdominant	A/A-G/G	295 (56.8)	130 (56)	1.00
	A/G	224 (43.2)	102 (44)	1.09 (0.76-1.55)
Additive		-	-	0.97 (0.75-1.27)
<i>GSTT1</i>				
	+/+	573 (77.6)	192 (82.8)	1.00
	0/0	165 (22.4)	40 (17.2)	0.65 (0.43-0.98) ^a
<i>GSTM1</i>				
	+/+	385 (52.2)	100 (43.1)	1.00
	0/0	353 (47.8)	132 (56.9)	1.45 (1.06-2.00) ^a

¹OR adjusted for age, gender, and alcohol and smoking habits and polymorphisms; ^a*P* < 0.05 vs control. OR: Odds ratio.

Individual polymorphism analysis

GSTM1 null genotype carriers had a higher risk of developing the disease (OR = 1.45; 95%CI: 1.06-2.00; *P* = 0.022). On the other hand, the *GSTT1* polymorphism was associated with a reduced risk of SCRC (OR = 0.65; 95%CI: 0.43-0.98; *P* = 0.037; Table 1).

In the present study, there was a significant interaction between the presence of the wild-type allele of the *GSTP1* Ile105Val polymorphism and smoking habit on the risk of SCRC (OR = 2.33; 95%CI: 1.34-4.05; *P* = 0.049). However, there was no interaction between the other polymorphisms and smoking or drinking habits on the risk of the disease (Table 2).

With regard to the clinical-histopathological parameters of the SCRC samples, the rectum was the most frequent primary site (60%), in addition to aggressive tumors (69.65%; Table 3). There was an association between the *GSTM1* null genotype and the presence of aggressive tumors (OR = 2.33, 95%CI: 1.23-4.41; *P* = 0.0087).

Analysis of the combined polymorphisms

An increased risk of SCRC was observed in the presence of the combination of the *GSTT1* non-null/*GSTM1* null genotypes (OR = 1.50; 95%CI: 1.03-2.19; *P* = 0.033) and the *GSTT1* non-null/*GSTM1* null/*GSTP1* Val* (*with the presence of at least one polymorphic

allele) (OR = 1.85; 95%CI: 1.01-3.36; *P* = 0.045). The combined *GSTT1* non-null/*GSTM1* null genotypes (OR = 2.40; 95%CI: 1.19-4.85; *P* = 0.015) and *GSTT1* non-null/*GSTM1* null/*GSTP1* Val* (OR = 2.92; 95%CI: 1.05-8.12; *P* = 0.040) were associated with tumor progression (Table 4).

Survival analysis

Kaplan-Meier curve analysis showed that the survival time of carriers of the polymorphic allele *GSTP1* Ile105Val, and the *GSTM1* and *GSTT1* null genotypes, were not significantly different from the survival time of non-carriers of these polymorphisms (Table 5).

DISCUSSION

In the present study, it was observed that individuals with advanced age (≥ 62 years) were more susceptible to SCRC, which is consistent with previous reports where old age was considered to be an etiological factor for this tumor type^[2,24]. In terms of gender, women are more susceptible to SCRC. Other studies have observed a similar trend in gender among patients with SCRC and the control group^[25-27]. An increase in the number of cases among women due to an increase in cigarette smoking and alcohol consumption has been observed^[28,29]. It is important to note that the group

Table 2 Interaction between polymorphisms in the genes *GSTP1*, *GSTT1*, and *GSTM1* and smoking or alcohol habits on the risk of sporadic colorectal cancer

	Tobacco consumption						Alcohol consumption					
	Non-smoker			Smoker			Non-smoker			Smoker		
	Case	Control	OR ¹ (95%CI)	Case	Control	OR ¹ (95%CI)	Case	Control	OR ¹ (95%CI)	Case	Control	OR ¹ (95%CI)
<i>GSTP1</i>												
A/A	50	136	1.00	57	91	2.33 (1.34-4.05) ^a	59	116	1.00	48	111	1.31 (0.74-2.31)
A/G-G/G	80	177	1.40 (0.87-2.27)	45	115	1.59 (0.91-2.77)	73	147	1.12 (0.69-1.81)	52	145	1.19 (0.70-2.04)
<i>GSTT1</i>												
+/+	110	362	1.00	82	211	1.42 (0.98-2.08)	108	300	1.00	84	273	0.76 (0.52-1.12)
0/0	20	103	0.60 (0.34-1.04)	20	62	1.03 (0.57-1.88)	24	95	0.63 (0.37-1.07)	16	70	0.53 (0.28-1.01)
<i>GSTM1</i>												
+/+	52	231	1.00	48	154	1.40 (0.86-2.28)	56	206	1.00	44	179	0.76 (0.46-1.26)
0/0	78	234	1.38 (0.90-2.10)	54	119	2.19 (1.34-3.57)	76	189	1.42 (0.93-2.18)	56	164	1.14 (0.72-1.82)

¹OR adjusted for age, gender, alcohol and smoking habits and polymorphisms; ^a $P < 0.05$ vs control. OR: Odds ratio.

of women with SCRC evaluated in this study had a mean age of 62 ± 13 years, which may suggest that hormonal factors might contribute to SCRC. Some studies have associated postmenopausal state with the incidence of colorectal cancer in women^[30-32]. In addition, hormone replacement therapy has been proved to be a protective factor for SCRC^[33-36]. A meta-analysis demonstrated an association between the protective effect of soy estrogen in women with SCRC who were postmenopausal^[37].

Smoking and drinking habits were not associated with SCRC in the present study. On the other hand, Koh *et al.*^[38] observed a threefold increased risk of colorectal cancer among smokers compared to those who had never smoked. Some data on the risk of SCRC due to alcohol consumption are inconsistent, which can be explained by the variation in the amount of alcohol consumption analyzed in the different studies^[39,40]. Analysis of the HWE revealed that the *GSTP1* Ile105Val polymorphism was in equilibrium in both the case and control groups. This result was similar to that observed by other studies in SCRC^[26,41]. With regard to the *GSTT1* and *GSTM1* polymorphisms, the HWE test was not possible because the molecular analysis did not distinguish wild-type homozygous and heterozygous individuals^[25].

In the present study, the *GSTP1* gene polymorphism showed no association with SCRC, corroborating other investigations in Bulgarian and Chinese populations^[3,25,27,42]. However, one study in a Tunisian population observed a significant difference in the frequency of polymorphisms between the case and control groups and was associated with the risk of SCRC^[26]. A single study observed a reduced risk of SCRC in the presence of the *GSTP1* Ile105Val polymorphism; however, there are no consistent data to explain the biological relevance of this finding^[16].

The *GSTP1* gene polymorphism results in an alteration of the amino acid sequence of the protein and a consequent reduction in enzymatic activity and inefficient detoxification^[43]. However, although the *GSTP1* Ile105Val polymorphism was not associated with SCRC in this study, the level of expression of this gene may be an important factor, which is not dependent on this genetic change. A hepatocellular carcinoma (HCC) study found that increased *GSTP1* gene expression *in vivo* and *in vitro* resulted in reduced cell proliferation in tumor cells, inhibition of Akt phosphorylation, and cell cycle disruption in G1/S by increasing p21 and p27 cell cycle inhibitors^[44]. High *GSTP1* expression was also associated with better prognosis in patients with HCC^[44]. In addition, hypermethylation of *GSTP1* has been observed in several types of cancers, such as prostate, breast, lung, and liver cancers^[45].

In relation to the *GSTT1* and *GSTM1* gene polymorphisms, the *GSTT1* null genotype was associated with a reduced risk of the development of SCRC, whereas the presence of the *GSTM1* null genotype was associated with increased risk of SCRC. The absence of some of the GST isoenzymes in normal colorectal mucosa resulting from null genotypes such as the presence of the *GSTM1* polymorphism may alter the major detoxification function of GSTs in the metabolism of xenobiotics^[4]. In Chinese and Iranian populations, an increased risk of SCRC in the presence of *GSTT1* and *GSTM1* null genotypes was determined^[2,5,46]. On the other hand, other studies did not find an association between *GSTT1* and *GSTM1* null genotypes with SCRC^[3,16,26,46-49]. In a case-control study, Vlaykova *et al.*^[4] found no association between *GSTM1* null genotype and the risk of SCRC, but the *GSTT1* null genotype was associated with an increased risk of SCRC. These different results may be related to the time of

Table 3 Distribution of the clinical-histopathological parameters in relation to the polymorphisms in the genes *GSTP1*, *GSTT1*, and *GSTM1* in patients with colorectal cancer *n* (%)

Models	Genotypes	Tumor progression (TNM) (<i>n</i> = 201)				Primary site			
		Non-advanced 61 (31)	Advanced 140 (69)	OR ¹	95%CI	Colon	Rectum	OR ¹	95%CI
<i>GSTP1</i>									
Codominant	A/A	31 (51)	62 (44)	1.00		42 (46)	65 (46)	1.00	
	A/G	23 (38)	65 (47)	1.37	(0.70-2.66)	38 (41)	64 (45)	0.96	(0.54-1.72)
	G/G	6 (10)	11 (8)	1.14	(0.37-3.50)	11 (12)	12 (8)	0.73	(0.29-1.85)
Dominant	A/A	31 (51)	62 (44)	1.00		42 (46)	65 (46)	1.00	
	A/G-G/G	29 (48)	76 (55)	1.32	(0.71-2.48)	49 (53)	76 (53)	0.91	(0.53-1.57)
Recessive	A/A-A/G	54 (90)	127 (92)	1.00		80 (87)	129 (91)	1.00	
	G/G	6 (10)	11 (8)	1.00	(0.34-2.95)	11 (12)	12 (8)	0.74	(0.31-1.81)
Overdominant	A/A-G/G	37 (61)	73 (52)	1.00		53 (58)	77 (54)	1.00	
	A/G	23 (38)	65 (47)	1.34	(0.70-2.56)	38 (41)	64 (45)	1.02	(0.59-1.77)
Aditivo	-	-	-	1.18	(0.73-1.92)	-	-	0.89	(0.59-1.34)
<i>GSTT1</i>									
	+/+	47 (78)	47 (78)	1.00		78 (85)	114 (80)	1.00	
	0/0	13 (22)	20 (14)	0.57	(0.26-1.27)	13 (14)	27 (19)	1.47	(0.71-3.06)
<i>GSTM1</i>									
	+/+	34 (56)	53 (38)	1.00		45 (49.5)	55 (39)	1.00	
	0/0	26 (43)	85 (61)	2.33	(1.23-4.41) ^a	46 (50.5)	86 (61)	1.49	(0.87-2.57)

¹OR adjusted for age, gender, alcohol and smoking habits and polymorphisms; ^a*P* < 0.05 vs control. OR: Odds ratio.

exposure to environmental factors and the population heterogeneity.

It has been observed that the effect of GST polymorphisms, when combined, may increase the risk of SCRC two- or threefold^[41]. The present study demonstrated that combinations of *GSTT1* non-null/*GSTM1* null genotypes and *GSTT1* non-null/*GSTM1* null/*GSTP1* Val* (presence of at least one polymorphic allele) are associated with an increased risk of SCRC and tumor progression. These findings corroborate the results of individual analyses of polymorphisms, which indicate the influence of the *GSTT1* non-null genotype on SCRC because the null genotype was associated with a reduced risk of the disease.

In the Indian population, an association between the *GSTM1* null/*GSTT1* null genotypes and the combination of *GSTM1* null/*GSTT1* null/*GSTP1* Val* and the risk of SCRC was observed^[41]. This result was also observed in a study by Vlaykova *et al.*^[4] in the Bulgarian population. A study in the Turkish population found an association between the *GSTT1* null/*GSTM1* non-null genotypes and *GSTT1* null/*GSTM1* non-null/*GSTP1* Ile (wild-type homozygote) and SCRC^[3]. Cong *et al.*^[25] observed an increased risk in the presence of *GSTT1*/*GSTM1* genotypes, whereas the combination of *GSTT1* non-null/*GSTM1* null genotypes resulted in a significant reduced risk of SCRC, differing from the findings of this and other studies. On the other hand, other studies that analyzed the effect of the combined genotypes *GSTT1*/*GSTM1* did not find an association with the risk of SCRC^[26,47,48]. Several studies have evaluated the potential association between SCRC and the combined genotypes of these polymorphisms. The observed results vary, indicating the importance of studying the

effects of the genotypic combination in SCRC.

In the present study, a significant interaction between the presence of the wild-type allele of *GSTP1* Ile105Val polymorphism and smoking habit on the risk of SCRC was demonstrated. Differing from the results of the present study, a study in the Chinese population found no interaction between the *GSTP1* Ile105Val and smoking habit or drinking habit on the risk of SCRC^[38]. The literature is sparse in terms of studies evaluating the interaction between risk factors and the *GSTP1* Ile105Val polymorphism in the development of SCRC. The biological relevance of this finding is unclear as the presence of at least one polymorphic allele of the *GSTP1* gene combined with the nullity of *GSTM1* and the presence of the *GSTT1* allele were associated with increased risk of SCRC. In addition, smoking habit was not associated with this tumor type in the present study.

With regard to the *GSTT1* and *GSTM1* polymorphisms, this study did not find an association between smoking or drinking habits and the risk of SCRC. These results are in accordance with two other studies in a Korean and Japanese population^[46,48]. The study by Piao *et al.*^[49] did not show a relationship between drinking habit and the *GSTT1* and *GSTM1* null genotypes on the risk of SCRC. However, a study in Singapore found an increased risk for smokers carrying at least two null genotypes that caused low enzyme activity^[38].

The controversial results regarding these polymorphisms may suggest that other genes involved in the metabolism of xenobiotics may be more relevant in the development of SCRC, such as polymorphisms in genes acting on phase I xenobiotic metabolism^[27,50]. Although the polymorphisms studied change in order to reduce or eliminate the enzymatic activity, other genes can also act, compensating for the detoxification of the

Table 4 Association between the double combined *GSTT1/GSTM* genotypes and triple combined *GSTT1/GSTM/GSTP1*, colorectal cancer, tumor progression, and primary site, adjusted for gender, age, smoking, and alcohol consumption

	Case (n = 198)	Colorectal cancer			Tumor progression (TNM) (n = 198)			Primary site				
		Control (n = 738)	OR ¹	95%CI	Non-advanced (n = 60)	Advanced (n = 138)	OR ¹	95%CI	Colon (n = 81)	Rectum (n = 117)	OR ¹	95%CI
Double combination of genotypes												
<i>GSTT1</i>												
(+)	68	303	1.00		26	42	1.00		34	34	1.00	
(-)	97	270	1.50	(1.03-2.19) ^a	21	76	2.40	(1.19-4.85) ^a	36	61	1.67	(0.88-3.18)
(+)	19	82	1.00	(0.55-1.84)	8	11	0.74	(0.26-2.15)	7	12	1.70	(0.59-4.94)
(-)	14	83	0.61	(0.32-1.19)	5	9	1.20	(0.35-4.10)	4	10	2.60	(0.72-9.46)
Triple combination of genotypes												
<i>GSTT1</i>												
(+)	32	96	1.00		12	20	1.00		16	10	1.00	
(-)	36	126	1.13	(0.61-2.10)	14	22	0.93	(0.34-2.56)	12	17	1.81	(0.67-4.92)
(+)	10	22	1.45	(0.56-3.77)	5	5	0.50	(0.12-2.18)	18	22	1.41	(0.33-5.98)
(-)	9	34	0.90	(0.36-2.25)	3	6	1.07	(0.21-5.31)	2	7	4.57	(0.80-26.24)
(+)	42	86	1.52	(0.81-2.83)	8	22	1.78	(0.65-4.86)	11	19	2.58	(0.99-6.75)
(-)	55	98	1.85	(1.01-3.36) ^a	10	42	2.92	(1.05-8.12) ^a	19	33	2.06	(0.83-5.15)
(+)	9	23	1.27	(0.48-3.40)	3	5	1.25	(0.25-6.19)	1	7	5.47	(0.92-32.60)
(-)	5	34	1.27	(0.11-1.08)	1	3	1.01	(0.14-7.42)	2	2	1.88	(0.27-13.33)

¹OR adjusted for age, gender, alcohol and smoking habits and polymorphisms; ^ap < 0.05 vs control; *Ile/Val ou Val / Ile. OR: Odds Ratio.

substances present in tobacco and alcohol.

With regard to the clinical-histopathological parameters of SCRC, some studies have shown that low activity GST genotypes can be associated with more aggressive tumors and survival in colorectal cancer patients^[51,52]. An association between the *GSTM1* null genotype and the presence of advanced tumors has been observed. One study demonstrated an association between aggressive tumors and the presence of the *GSTT1* null genotype^[47]. However, other studies that evaluated the same polymorphisms did not find an association between the polymorphic genotypes and the clinical- histopathological parameters of SCRC^[3,27,42,49].

This biological relationship between GST and progression is still not well described. However, a possible explanation for this is that GSTs play important roles in the regulation of genes related to activation of cellular maintenance, proliferation and apoptosis evasion. Thus, GSTs interact with tumor necrosis factor (TNF) receptor associated factor 2 (TRAF2) and decrease signal transduction from receptors in the TNF alpha-like (TNF-g) and c-Jun NH2-terminal kinase (JNK kinase) pathways^[12,53,54]. No association between polymorphisms and the primary sites of SCRC were identified in the present study. In accordance with these findings, the study by Vlaykova *et al*^[41] did not find an association between polymorphisms of *GSTT1* and *GSTM1* null genotypes and the primary site. However, Wang *et al*^[41], observed an increased risk of rectal cancer in the presence of the *GSTM1* null genotype, while the *GSTT1* null genotype was associated with a risk of colon cancer.

It is worth noting that predisposition to SCRC is multifactorial and results from the interaction between allelic variants of low-penetrance genes and environmental factors such as advanced age, eating habits, and smoking and drinking habits^[3,55,56]. Therefore, the findings regarding the modulation of susceptibility to SCRC in the presence of the polymorphisms analyzed, regardless of smoking or drinking habits, reinforce the influence of these polymorphisms on the etiology of SCRC, even though they do not influence patient survival. These results may contribute to the understanding of the mechanisms involved in colorectal carcinogenesis.

In conclusion, females with advanced age are more susceptible to SCRC. The presence of the *GSTM1* null genotype is associated with an increased risk of SCRC. The *GSTM1* null genotype is associated with tumor progression. The combination of *GSTT1/GSTM1* and *GSTT1/GSTM1/GSTP1* genotypes are associated with

Table 5 Polymorphisms *GSTT1*, *GSTM1*, and *GSTP1* in relation to overall survival of colorectal cancer patients

Polymorphisms	Survival (5 yr)
<i>GSTT1</i>	
Positive	64
Negative	68
<i>GSTM1</i>	
Positive	67
Negative	63
<i>GSTP1</i> A313G	
AA	61
AG	70
GG	63

^a*P* < 0.05 vs control.

an increased risk of SCRC and tumor progression. Polymorphisms are not associated with the overall survival rate of SCRC patients.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer is the third most common cancer worldwide and develops on the inner walls of the colon and rectum. Genetic and environmental factors may increase the risk of colorectal cancer *via* the metabolism of carcinogens. Therefore, the evaluation of polymorphisms in genes involved in this process may help to modulate the development of colorectal cancer. Polymorphisms in genes encoding *GSTP1*, *GSTT1*, and *GSTM1* may alter enzymatic activity. This change can lead to DNA damage and deregulation of the mechanisms involved in colorectal cancer.

Research motivation

Polymorphisms in the coding genes *GSTP1*, *GSTT1*, and *GSTM1* have been studied in terms of susceptibility to diseases such as cancer. However, the literature presents conflicting results. Therefore, several studies are needed to assess and confirm the role of factors that influence changes in metabolic processes related to colorectal cancer.

Research objectives

The main objective of this study was to evaluate the influence of polymorphisms in the *GSTP1*, *GSTT1* and *GSTM1* genes on the risk of colorectal cancer. The data showed that carriers of polymorphisms in the *GSTM1* genes and the combination of *GSTT1* non-null/*GSTM1* null genotypes and *GSTT1* non-null/*GSTM1* null/*GSTP1* Val* (*with the presence of at least one polymorphic allele) constitute a risk group for sporadic colorectal cancer (SCRC), and polymorphisms in the *GSTM1* gene and the *GSTT1* non-null/*GSTM1* null combinations, *GSTT1* non-null/*GSTM1* null/*GSTP1* Val* increase the aggressiveness of the tumor. Thus, considering the high incidence of this cancer, it is important to understand the factors that lead to carcinogenesis in order to develop preventive and therapeutic strategies for the management of cancer.

Research methods

This case-control study evaluated 970 individuals, 232 cases and 738 controls, using multiplex polymerase chain reaction (PCR) and polymerase chain reaction-restriction fragment chain reaction (PCR-RFLP) polymorphism. Demographics are tabulated by percentage. The binary logistic regression model was used to evaluate the association of age, gender, smoking and eating habits with SCRC, and to evaluate the association of the Hardy-Weinberg equilibrium (HWE) with the Chi-square test. Multiple binary logistic regression, adjusted for age, gender and smoking and alcohol habits, was also used to evaluate the association between the genetic models of the polymorphisms and the development of SCRC. The dominant genotypic model was used to assess the interaction between polymorphisms and smoking habits, adjusted

for age, gender, and ethnicity, and to evaluate the interaction of polymorphisms and alcohol consumption, adjusted for age, gender and smoking, on the risk of SCRC. In addition, the Kapla-Meier curve was used to assess the overall survival of patients with SCRC.

Research results

The data showed that carriers of polymorphisms in the *GSTM1* genes and the combination of *GSTT1* non-null/*GSTM1* null genotypes and *GSTT1* non-null/*GSTM1* null/*GSTP1* Val* (*with the presence of at least one polymorphic allele) constitute a risk group for SCRC, and polymorphisms in the *GSTM1* gene and the *GSTT1* non-null/*GSTM1* null combinations, *GSTT1* non-null/*GSTM1* null/*GSTP1* Val* increase the aggressiveness of the tumor. Thus, considering the high incidence of this cancer, it is important to understand the factors that lead to carcinogenesis in order to develop preventive and therapeutic strategies for the management of cancer.

Research conclusions

Similar studies have not previously been performed in the Brazilian population. Therefore, this work is unprecedented in this population. In addition, we emphasize the importance of the association between female gender and susceptibility to SCRC as well as the survival analysis associated with the polymorphisms studied, which have not been extensively studied in the literature. Polymorphisms in the *GSTP1*, *GSTT1* and *GSTM1* genes were involved in carcinogenesis and the poor prognosis of SCRC. In the Brazilian population it was observed that females with advanced age were more susceptible to SCRC. The presence of the *GSTM1* null genotype, and the combination of *GSTT1*/*GSTM1* and *GSTT1*/*GSTM1*/*GSTP1* genotypes are associated with an increased risk of SCRC and tumor progression.

This study provides a perspective on biomarkers of GSTs related to the prognosis of SCRC that has not been extensively studied in other populations, especially the Brazilian population. These data may contribute to clinical practice. Another interesting fact was the association between females, age over 60 years and the risk of SCRC. Menopausal women (estrogen reduction) were also shown to be more susceptible to SCRC. Polymorphisms in the genes involved in the xenobiotic metabolism pathway are associated with the development and poor prognosis of SCRC.

In this study, statistical analyses were widely used, and unlike other studies, multiple logistic regression was performed to evaluate the interactions between the polymorphisms studied and variables. In addition, survival was assessed by Kaplan Meier analysis. These analyses are extremely relevant in studies involving population genetic polymorphisms.

An association between some polymorphisms of xenobiotic metabolism and the development and progression of SCRC was observed. Advanced age and female gender were associated with the development of SCRC and polymorphisms in the genes involved in the xenobiotic metabolism pathway were associated with the development and poor prognosis of SCRC. This study may contribute to GSTs being used as diagnostic and prognostic biomarkers for SCRC. These data together with the findings of other studies may contribute to the development of treatment strategies for SCRC.

Research perspectives

This study demonstrated the importance of population studies with a large sample size in research on polymorphisms. Thus, we intend to expand the sample size to validate the results and include more polymorphisms related to the xenobiotic pathways in order to better understand the roles of these pathways in SCRC carcinogenesis. Research methods such as real-time PCR, are important in order to accurately quantify the presence of polymorphisms.

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