The role of *GSTA2* polymorphisms and haplotypes in breast cancer susceptibility: A case-control study in the Portuguese population

SUSANA N. SILVA[1], ANA PAULA AZEVEDO[3], VALDEMAR TEIXEIRA[3],
JULIETA ESPERANÇA PINA[2], JOSÉ RUEFF[1] and JORGE FRANCISCO GASPAR[1]

Departments of [1]Genetics and [2]Laboratory Medicine, Faculty of Medical Sciences, New University of Lisbon,
Rua da Junqueira 96, 1349-008 Lisbon; [3]Department of Clinical Pathology, Hospital de S. Francisco Xavier,
Estrada do Forte do Alto do Duque 1495-005 Lisbon, Portugal

Abstract. Glutathione-S-transferases (GSTs) are a super-family of phase II metabolizing enzymes that catalyse the detoxification of a large range of endogenous and exogenous toxic compounds, playing an important role in protecting cells against damage, through glutathione conjugation with electrophilic substances. Polymorphic variation in these enzymes that affect its activity seems to be related to individual susceptibility to various human diseases, including cancer. Of the GST super-family, the alpha class GSTs have commonly been described as one of the most versatile class, since it is responsible for detoxification of compounds such as bilirubin, bile acids and penicillin, thyroid and steroid hormones, allowing its solubilization and storage in the liver. Among the alpha class, GSTA1 and GSTA2 isoforms are the most widely expressed in human tissues. Additionally, these enzymes can catalyse conjugation of the nitrogen mustard group of alkylating anticancer drugs, some heterocyclic amines and α,ß-unsaturated aldehydes. Since some risk factors for increased breast cancer risk could be related to high production of reactive oxygen species during the metabolism of estrogens by catechol estrogens, or to the exposure to genotoxic compounds, and some of these toxic compounds are usually metabolized by GSTA2, we carried out a hospital based case-control study in a Caucasian Portuguese population (291 breast cancer patients without familiar history of breast cancer and 547 controls matched for age, sex and ethnicity) in order to evaluate the potential modifying role of three non-synonymous polymorphisms in the *GSTA2* gene (P110S Ex 5+56C>T;, rs2234951; S112T Ex5+63G>C, rs2180314 and E210A Ex7+83A>C, rs6577) on the individual susceptibility to breast cancer. Our data show that the studied polymorphisms are in strong linkage disequilibrium, but no association was observed between individual *GSTA2* polymorphisms and haplotypes and individual susceptibility to breast cancer.

Introduction

Breast cancer is the main type of female cancer (about 182,460 new cases are estimated by the American Cancer Society for 2008, in the USA) and the second leading cause of cancer death in women (1). However, the etiology of this disease remains elusive, even though it is known that for a substantial fraction of breast cancer cases, the age at the first child's birth, parity, menopausal age (i.e. reproductive and hormonal factors) and family history, are well-established risk factors.

The hereditary fraction of this pathology accounts for 5-10% of all breast cancer cases (2,3), with BRCA1 and BRCA2 having been identified as the two main susceptibility genes from familial linkage studies (3). Even though mutations in these genes are highly associated with inherited predisposition, somatic mutations in these genes are rare in sporadic breast cancer cases.

The majority of the risk factors, mainly related to sporadic cases, point to an association with prolonged exposure to increased levels of estrogens (4,5). Several epidemiological studies have been published showing that circulating estrogens may contribute to an increased risk of breast cancer. Furthermore, during the metabolism of estrogen some carcinogenic metabolites can be produced, such as cathecol estrogens (6-8). These metabolites could be responsible for an increased production of Reactive Oxygen Species (ROS), leading to disruption of cellular redox homeostasis (7,8) and DNA lesions. It is postulated that the genotoxic consequences of the oxidative estrogen metabolism pathway is mitigated by conjugation reactions of the metabolites with phase II enzymes (8). Several enzymes are involved in the oxidative metabolism and conjugation of estrogens (7), suggesting a potential

Correspondence to: Dr Jorge Francisco Gaspar, Department of Genetics, Faculty of Medical Sciences, New University of Lisbon, Rua da Junqueira 96, P-1349-008 Lisbon, Portugal
E-mail: jgaspar.gene@fcm.unl.pt

involvement of the polymorphic forms of their genes in breast cancer susceptibility.

One of the enzymatic families involved in Phase II metabolism (6,7,9,10) is the highly polymorphic Glutathione S-Transferase (GSTs) super family which is responsible for carcinogen detoxification by conjugation with reduced glutathione (GSH) of numerous reactive metabolites, including by-products of oxidative stress (11) and metabolites generated through the oxidative estrogen metabolism pathway (6,8). Some of these metabolites include estrogen quinones that undergo conjugation with GSH through the catalytic action of GSTP1. The formation of GSH-estrogen conjugates would reduce the level of estrogen quinones and thereby lower the potential for DNA damage (8).

The alpha class GSTs are strongly expressed in liver, kidney and adrenal tissue, and have commonly been described as one of the most versatile GST families, since it is responsible for GSH conjugation of compounds such as bilirubin, bile acids and penicillin, thyroid and steroid hormones, allowing their solubilization and storage in the liver (12). Additionally, the conjugation of the nitrogen mustard group of alkylating anticancer drugs, of some heterocyclic amines and α,ß-unsaturated aldehydes also leads to detoxification (12,13). GSTA1 and GSTA2 are the most expressed alpha GSTs enzymes in the liver (14,15), but they are also expressed in the human breast (15). There are few epidemiological studies relating the role of polymorphic alpha class GST in cancer susceptibility (16,17), especially in breast cancer (15). Since the Alpha family is involved in a wide range of roles that include steroid biosynthesis and providing protection against alkylating agents, polymorphic variations in these genes could be responsible for physiological consequences that could alter the susceptibility to disease and drug response (12). Two members of this class, *GSTA1* and *GSTA2* (usually co-expressed), catalyze the GSH conjugation of a wide variety of electrophiles, possess glutathione-dependent steroid isomerase activity, and glutathione-dependent peroxidase activity (14). The *GSTA2* gene is believed to represent a major line of defense against oxidative stress (18).

To date, some epidemiological studies, regarding breast cancer susceptibility, have been carried out focusing on several polymorphic families of GSTs, mostly the *GSTT1*, *GSTM1* and *GSTP1* genes (6,19-26). Other GST families have been less studied, and there is a scarcity of results regarding the influence of the alpha class with breast cancer susceptibility. Since the *GSTA2* gene is involved in the detoxification of metabolites associated with an increase risk to breast cancer, we carried out a hospital based case-control study in a Caucasian Portuguese population in order to evaluate the potential modifying role of the non-synonymous polymorphisms in the *GSTA2* gene (P110S Ex 5+56C>T;, rs2234951; S112T Ex5+63G>C, rs2180314 and E210A Ex7+83A>C, rs6577) on the individual susceptibility to breast cancer.

Materials and methods

Study subjects. This study includes 291 Caucasian breast cancer female patients, recruited at São Francisco Xavier Hospital (Department of Laboratory Medicine), without previous history of neoplasic disease, thyroid pathology and blood transfusions. Histological diagnosis was confirmed in all the cases. The control population (n=547) matched for sex and ethnicity, with no previous or concurrent malignant disease, was recruited at the same hospital where they were observed for non-malignant pathology. The anonymity of the patients and control population was guaranteed, and all studies were conducted with the written informed consent of all the individuals involved, obtained prior to blood withdrawal. Information on demographic characteristics, family history of cancer, lifestyle habits (e.g. smoking, alcohol drinking) was collected using a questionnaire administered by trained interviewers. Former smokers were defined as those who gave up smoking two years before cancer diagnosis or two years before the inclusion date as corresponding matched case. The response rate was higher than 95% for cases and controls.

DNA extraction. Blood samples of all patients and controls were collected into 10 ml heparinized tubes and stored at -20˚C until use. Genomic DNA was obtained from 250 μl of whole blood using a commercially available kit according to the manufacturer instructions (QIAamp DNA extraction kit; Qiagen, Hilden, Germany). Each DNA sample was stored at -20˚C until analysis.

Genotyping GSTA2 P110S, S112T and E210A gene polymorphisms. The genotyping of E210A polymorphism was determined by PCR-RFLP. The primers and PCR conditions for the polymorphic sites of this SNP are shown in Table I. This polymorphism results in either gain or loss of restriction sites, which therefore allowed the wild-type and variant alleles to be discriminated by RFLP after appropriate restriction enzyme digestion. After amplification, 10 μl of each PCR products were digested with appropriate restriction enzymes and eletrophoresed in 4% agarose gel with ethidium bromide (0.5 μg/ml) for visualization under ultraviolet light. The expected product for each genotype of the tested SNP is shown in Table I. All the genotype determinations were carried out twice in independent experiments and inconclusive samples were reanalysed.

The P110S and S112T polymorphisms were genotyped by real-time PCR (AB7300) using TaqMan SNP Genotyping Assays from Applied Biosystems (ABI Assays reference: C_12027714_50 and C_22275149_30, respectively) according to the manufacturer's instructions. To carry out the allelic discrimination the DNA samples were quantified by PicoGreen dsDNA Quantification Reagent (Molecular Probes, Eugene, OR, USA) according to the manufacturer's recommendations.

Statistical analysis. Genotypic frequencies and the analysis of Hardy-Weinberg frequencies for the different polymorphisms studied, in the control and patients populations, were carried out using Mendel software (27).

The degree of linkage disequilibrium between the different SNPs expressed as D', and the haplotype estimation for the combination of the different SNPs studied were calculated using SNPStats software (28).

The χ^2 test was used to evaluate the differences in genotype frequency, smoking status and alcohol consumption

Table I. PCR-RFLP details for *GSTA2* (E210A) polymorphism.

GSTA2	Primer sequence	Temp. (˚C)	PCR product (bp)	Effect on enzyme restriction site	Patterns after enzyme restriction enzyme digestion
E210A	Forward 5'-CCAAggAAgCCTCCCATgCATg-3' Reverse 5'-gCTTCACAACAggCACAATCAACAC-3'	62	163	A→C creat one *Pae*I restriction site	AA: 163bp; AC: 163, 140, 23bp; CC: 140, 23bp

Table II. General characteristics of breast cancer cases (n=291) and control (n=547) populations studied.

Characteristics	Cases n (%)	Controls n (%)	P-value[d]
Age[a,b]			
≤30	1 (0.3)	2 (0.4)	
31-49	68 (23.4)	120 (21.9)	0.921[c]
50-69	161 (55.3)	300 (54.8)	
≥70	61 (21.0)	125 (22.9)	
Smoking habits			
Never and former	254 (87.9)	490 (91.6)	
Current	35 (12.1)	45 (8.4)	0.087[c]
Missing	2	12	
Alcohol habits			
Never	221 (76.2)	441 (82.6)	
Social	25 (8.6)	59 (11.0)	<0.0001[c]
Regular	44 (15.2)	34 (6.4)	
Missing	1	13	

[a]Age of cases at diagnosis; [b]age of control population at the time of diagnosis for the matched case; [c]cases vs. control group; [d]see Materials and methods.

distributions between cases and controls. The Kolmogorov-Smirnov test was used in order to verify the normality of the continuous variables (e.g. age) and the Levene test was used to analyse the homogeneity of variances.

The crude and adjusted odds ratio (OR) and the corresponding 95% confidence intervals (CI) were calculated using unconditional multiple logistic regression. The model for adjusted OR included terms for age at diagnosis (≤30, 31-49, 50-69 and ≥70 years), the lower age group being the reference class; alcohol consumption (never, social and regular drinkers) non-drinkers being the reference group, and smoking habits (smokers/non smokers), non-smokers being the reference group. All analyses were performed with an SPSS statistical package (version 15.0) (SPSS Inc. Chicago, IL).

Results

Two-hundred and ninety-one breast cancer patients and 547 age-matched controls in this Portuguese case-control study were included. The main characteristics (age, smoking and alcohol habits) for both populations are shown in Table II. No significant differences for age and smoking habits were found

between cases and controls. However, alcohol drinkers are more prevalent among breast cancer patients than in the control population.

We included in this study 3 SNPs present in the *GSTA2* gene (P110S, S112T and E210A), all non-synonymous. All the SNPs are in Hardy-Weinberg equilibrium and in Table III are depicted the Minor Allele Frequency (MAF), and genotype frequencies in both populations. MAF values obtained were in accordance with the ones reported in the HapMap project (http://www.hapmap.org/). The data available in the literature in Caucasian populations, the genotype frequencies for the *GSTA2* S112T polymorphism and the values reported in these studies are ambiguous, two of them are in agreement with the data obtained in this study (16,29), while further two studies report different frequencies (17,30). The SNP frequencies in control and cancer population are not significantly different and the crude and adjusted ORs associated with each polymorphism are not significantly different (Table III), suggesting that these polymorphisms are not associated with breast cancer susceptibility. The ORs associated with the different SNPs studied after stratification for different breast cancer status, that could be relevant as

Table III. Genotype distribution and breast cancer risk to the polymorphisms studied (*GSTA2* P110S, S112T and E210A) in cases and control population.

Genotype	Cases n (%)	Controls n (%)	MAF		Crude OR (95% CI)	Adjusted OR (95% CI)[a]
			Cases	Controls		
P110S (Ex5+56C>T)						
CC	265 (91.7)	505 (92.8)			1 (Reference)	1 (Reference)
CT	24 (8.3)	39 (7.2)			1.173 (0.690-1.992)	1.218 (0.705-2.104)
			T: 0.0415±0.0083	T: 0.0358±0.0056		
TT	-	-				
Missing	2	3				
S112T (Ex5+63G>C)						
GG	92 (31.8)	155 (28.5)			1 (Reference)	1 (Reference)
GC	146 (50.5)	280 (51.6)			0.878 (0.634-1.218)	0.873 (0.625-1.219)
			C: 0.4291±0.0206	C: 0.4567±0.0151		
CC	51 (17.6)	108 (19.9)			0.796 (0.522-1.212)	0.770 (0.501-1.184)
Missing	2	4			-	-
E210A (Ex7+83A>C)						
AA	257 (88.6)	485 (88.7)			1 (Reference)	1 (Reference)
AC	33 (11.4)	61 (11.2)			1.017 (0.649-1.594)	1.008 (0.635-1.601)
CC	0 (0)	1 (0.2)	C: 0.0569±0.0096	C: 0.0576±0.007	ND	ND
AC + CC	33	62			1.001 (0.639-1.567)	0.989 (0.623-1.569)
Missing	-	-			-	-

[a]ORs were adjusted for: age at diagnosis (≤30, 31-49, 50-69 and ≥70), the lower age group being the reference class; alcohol consumption (never, social and regular drinkers), never drinkers being the reference class, and smoking habits (smokers/non-smokers), non-smokers being the reference class.

Table IV. Linkage disequilibrium coefficient D' between the three studied SNPs.

SNP	P110S	S112T	E210A
P110S	-	0.8992	0.9665
S112T	-	-	0.9696
E210A	-	-	-

potential risk factors (i.e. breast feeding, menopausal age, menarche age, parity, age at first full-term pregnancy), were undertaken and did not reveal any potential association with disease either (data not shown). The linkage disequilibrium analysis was determined using SNPStats software, and demonstrates that all SNPs evaluated in this study are in linkage disequilibrium, measured by D' values as depicted in Table IV.

The combination of the different alleles of the GSTA2 gene could potentially generate eight different haplotypes, but haplotype estimation with the data obtained in our study only reveal the existence of six different haplotypes (Table V), four of them were previously described by Tetlow *et al* in Australian, Bantu African, Creole African and Chinese

Table V. *GSTA2* haplotype frequencies in Portuguese population estimated by SNPStats software.

Haplotype estimation	Haplotype frequencies	
	Cases	Controls
GSTA2 (P110; S112; E210)[a]	0.5713	0.5387
GSTA2 (P110; S112; A210)[a]	NA	0.00140
GSTA2 (P110; T112; E210)[a]	0.3303	0.3679
GSTA2 (S110; S112; E210)[a]	NA	0.003
GSTA2 (P110; T112; A210)	0.0567	0.0562
GSTA2 (S110; T112; E210)	0.0418	0.0328

[a]Haplotypes also identified by Tetlow *et al* (13).

populations (12,13). From the different haplotypes generated by the *GSTA2* non-synonymous polymorphism two of them (P110; S112; E210 and P110; T112; E210) (see Table V) have a cumulative frequency higher than 90% in both populations studied, and each one with a similar frequency in both populations. Accordingly, the data obtained concerning the

role of these haplotypes in breast cancer susceptibility do not reveal any significant association with the disease (data not show).

Discussion

There is a lack of data on the role of GSTA2 polymorphisms in human cancers. The data published until now has been mainly focused on *GSTA2* genomic organization, its expression in different tissues (31-33) and functional characterization of the *GSTA2* polymorphisms (12,13,17,34,35).

Several polymorphisms in *GSTA2* gene were described by Tetlow *et al* in three different ethnic populations. Some functional studies developed to evaluate the protein activity of variants generated by multiple polymorphisms, report in all but one haplotype [GSTA2 (S110; S112; E210)] no significant discrepancy in protein activity when compared with the more frequent haplotype [GSTA2 (P110; S112; E210)] (12,13,17). In fact, the variant form has a lower activity towards the conjugation of several substrates, such as Cumene hydroperoxide (12), suggesting that individuals with the S110 variant may have an increased susceptibility to disease related with oxidative stress. Additionally, the GSTA2 is also involved in the isomerization of Δ^5-androstene-3,17-dione, a precursor of several steroid hormones, such as progesterone. The variant form of *GSTA2* S110 also shows a lower activity towards this substrate, suggesting that individuals carrying this variant might have lower levels of steroid hormones. These studies structurally characterized the polymorphisms of human glutathione S-transferase alpha class, showing that S112T and E210A amino acid residues are not in the active site. The change S112T is conservative (both residues are polar non-charged) and did not show a dramatic effect on protein structure, while E210A is non-conservative (A residue is a small polar and E a large acidic residue), although this residue position could have a slight effect on protein function. Concerning the P110S it was shown that the substitution of a hydrophobic residue, non-polar (Pro), by a hydrophilic, uncharged polar residue (Ser), might both reduce the rigidity of the active site related to the loss of a structural residue, and increase hydrophilicity (12).

We performed a comprehensive study to analyze the possible role of 3 common non-synonymous polymorphisms (P110S; S112T; E210A) of *GSTA2* gene in the genetic susceptibility to breast cancer, which, to our knowledge, is the first study relating breast cancer with these polymorphisms. However, our results did not reveal any association of the different *GSTA2* polymorphisms evaluated and individual susceptibility to breast cancer (Table III). These results might be explained by the fact that the S112T and E210A polymorphisms do not lead to a significant decrease in the enzyme catalytic activity, and the polymorphism associated with changes in catalytic activity (*GSTA2* P110S), is only observed in heterozygosity, and with a frequency lower than 10% in both populations (cases and controls) (Table III). Regarding the molecular-epidemiological studies concerning *GSTA2* polymorphisms, no association between the *GSTA2* (S112T) polymorphism and the risk of colorectal cancer, malignant pleural mesothelioma (29,30) and prostate cancer (17) was described, but the variant allele of this poly-morphism seems to be associated with an increased risk of lung cancer (16). Additionally, our study reveals that all SNPs studied are in linkage disequilibrium. Through the combination of the different allelic variants of *GSTA2* non-synonymous polymorphisms, we obtained six different haplotypes in our populations (see Table V), which is in agreement with the data reported in previous studies (12,13). However, the results showed consistent differences on haplotype frequencies in other populations (12,13), that could be explained based on the basis of ethnic differences between populations.

Recent data from cancer studies have linked aberrant expression of GST isozymes with the development and expression of resistance to a variety of chemicals, especially the ones used as anticancer therapies. Studies in tumor tissues and chemotherapeutic-resistant tumor cell lines have shown overexpression of these enzymes (9,36). Further-more, studies in normal and cancer human breast tissue, showed that in most cases, the average level of GSTs was substantially elevated in the cancer tissues when compared with normal tissue, providing a plausible mechanism for the variable response to treatment (33).

Even though our data suggest that *GSTA2* polymorphisms are not associated with individual susceptibility to breast cancer risk, we cannot exclude that other SNPs in other genes associated with the detoxification might be involved in susceptibility to breast cancer. Additionally, we also cannot exclude that these polymorphisms might be associated with other aspects of oncologic disease such as drug resistance/patient survival, but further studies are required to evaluate this effect.

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