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EPIDEMIOLOGY

Association of *SULT1A1* Arg^{213}His polymorphism with male breast cancer risk: results from a multicenter study in Italy

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Abstract Male breast cancer (MBC) is rare and poorly understood. Like female breast cancer (FBC), MBCs are highly sensitive to hormonal changes, and hyperestrogenism, specifically, represents a major risk factor for MBC. MBC is considered similar to late-onset, post-menopausal estrogen/progesteron receptors positive FBC (ER+/PR+). Sulfotransferase 1A1 (SULT1A1) is an enzyme involved in the metabolism of estrogens. Recently, *SULT1A1* common functional polymorphism Arg^{213}His (638G>A) variant has been found to be associated with increased breast cancer (BC) risk, particularly in post-menopausal women. For this reason, we decided to explore whether *SULT1A1* Arg^{213}His could exert an effect on MBC development. The primary aim of this study was to evaluate the influence of the *SULT1A1* Arg^{213}His polymorphism on MBC risk. The secondary aim was to investigate possible associations with relevant clinical–pathologic features of MBC. A total of 394 MBC cases and 786 healthy male controls were genotyped for *SULT1A1* Arg^{213}His polymorphism by PCR–RFLP and high-resolution melting analysis. All MBC cases were characterized for relevant clinical–pathologic features. A significant difference in the distribution of *SULT1A1* Arg^{213}His genotypes was found between MBC cases and controls ($P < 0.0001$). The analysis of genotype-specific risk showed a significant increased MBC risk in individuals with G/A (OR 1.97, 95 % CI 1.50–2.59; $P < 0.0001$) and A/A (OR 3.09, 95 % CI 1.83–5.23; $P < 0.0001$) genotypes in comparison to wild-type genotype, under co-dominant model. A significant association between *SULT1A1* risk genotypes and HER2 status emerged. Results indicate that *SULT1A1* Arg^{213}His may

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act as a low-penetrance risk allele for developing MBC and could be associated with a specific tumor subtype associated with HER2 overexpression.

Keywords Male breast cancer · Estrogens · Estrogen receptor · Sulfotransferase 1A1 (SULT1A1) · *SULT1A1* Arg^{213}His polymorphism

Introduction

Male breast cancer (MBC) is a rare disease, representing less than 1 % of all breast cancers (BCs), with incidence rates of approximately 1 per 100,000 men per year [1]. MBC incidence trends are variable, with a minority of countries presenting evidence for an increase. Although outcomes for MBC have improved over time [2], morbidity and mortality in MBC patients are a serious concern.

MBC is likely to be caused by the concurrent effects of various risk factors: hormonal, environmental, and genetic. Like female breast cancer (FBC), MBC appears to be highly sensitive to hormonal changes. MBC is recognized as being primarily a hormone-dependent malignancy [3] and is widely accepted as an estrogen-driven disease specifically related to hyperestrogenism. An increased level of circulating estradiol appears to be an important factor in the etiology of the disease, and the mean total serum estradiol level is significantly increased in MBC patients compared with healthy males [4].

Family history of BC and personal history of cancer are also frequently observed in MBC patients [2], thus pointing to a relevant genetic component in MBC predisposition. Studies to date indicate mutations in the two major high-penetrance BC genes, *BRCA1* and, mainly, *BRCA2*, as having the most impact on MBC susceptibility, though only a small proportion (about 10 %) of MBCs is accounted for by mutations of these genes [5]. Thus, much of the genetic contribution to MBC risk remains to be elucidated. Current data based on age-frequency distribution, age-specific incidence rate patterns, and prognostic factors profiles suggest that MBC is similar to late-onset, post-menopausal estrogen/progesteron receptors positive (ER+/PR+) FBC. However, compared to FBC, MBC occurs later in life, with higher stage, lower grade, and more ER+/PR+ [2, 3].

Sulfotransferase 1A1 (SULT1A1) is one of the members of sulfotransferase (SULT) superfamily, considered to be the predominant type of SULTs because of its extensive tissue distribution and abundance [6]. Within the context, SULT1A1 catalyzes the sulfonation of estrogens to form biologically inactive estrogen sulfates, thus reducing the level of estrogens' exposure in target tissues, such as mammary tissue. The *SULT1A1* Arg^{213}His variant (rs9282861), is a very common functional polymorphism of the *SULT1A1* gene [7] and many studies have associated it with BC in women, though with contrasting results [8–13] Recent meta-analysis studies have shown that *SULT1A1* Arg^{213}His variant is associated with increased risk of BC, particularly in post-menopausal women [14–18]. *SULT1A1* Arg^{213}His variant (rs9282861) consists of a G to A transition at nucleotide 638 and causes an Arginine (Arg) to Histidine (His) substitution at aminoacid 213. Based on crystal structural modeling, it has been proposed that Arg^{213}His aminoacid substitution causes structural alteration in the SULT1A1 protein that affects the binding capacity to substrate [7]. A reduction of enzyme activity was demonstrated for individuals with homozygous ^{213}His allele variant, compared to those with Arg/Arg and Arg/His genotypes, and positive associations with high estrogens blood levels were found to be more pronounced among women carrying the His allele [12].

Given the role of *SULT1A1* in the metabolism of estrogens, the relevant role of estrogens in the pathogenesis of MBC, and the suggested similarity of MBC to post-menopausal BC, in which *SULT1A1* Arg^{213}His polymorphism has been recently associated with increased risk, we hypothesized that *SULT1A1* Arg^{213}His polymorphism might exert some effect on MBC risk. Therefore, the primary aim of our study was to evaluate the influence of the Arg^{213}His polymorphism on MBC risk, in a series of Italian cases and controls. A secondary aim was the investigation of possible associations with relevant clinical–pathologic features of MBC. To our knowledge, this is the first report investigating the association between *SULT1A1* polymorphism and MBC risk.

Materials and methods

Study population and data collection

The study was performed comparing a series of 394 MBC patients and 786 healthy male controls residing throughout Italy. Specifically, MBC cases and controls were recruited from ten Italian research hospitals geographically distributed throughout the country, all participating in the ongoing

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Italian Multicentre Study on MBC [19, 20]. The mean age at BC diagnosis was 61.5 years (SD 11.8) in MBC cases, and the mean age was 53.3 (SD 10.5) in the controls.

Information collected for each MBC case included: age at diagnosis, family and personal history of cancer, recurrence of disease, *BRCA1/2* mutational status, tumor histological type, grade, nodal status, ER, PR, MIB1, and HER2 expression.

Control samples were obtained from individuals enrolled under research or clinical protocols and from blood donors. Inclusion criteria: men with BC diagnosis, for MBC cases; and healthy males with residency within the same area as MBC cases, for control samples. All individuals in the control sample were Caucasian, but this was by chance (i.e., not a selection criterion). All participants signed an informed consent for the use of their biological samples for research purposes.

Procedures to maintain confidentiality for all the information collected were developed and strictly adhered to. The study was approved by Local Ethical Committee ("Sapienza" University of Rome, Prot. 264/12).

SNP genotyping

Buffy coat aliquots from MBC cases and controls were anonymously shipped to the research laboratory (Department of Molecular Medicine, Rome) where genomic DNA was extracted using QIAmp DNA Mini Kit (Qiagen Inc., Charlesworth, CA). *SULT1A1* $Arg^{213}His$ (G>A) polymorphism was analyzed by PCR–RFLP using the restriction enzyme *Hae*II (New England BioLabs, Ipswich MA) and by high-resolution melting (HRM) analysis performed with the 7,500 Fast Real-Time PCR (Applied Biosystems, Warrington, UK). Information on primers sequences is available on request. Samples from three individuals carrying the three *SULT1A1* $Arg^{213}His$ genotypes, respectively, were used as controls. In order to assess genotyping concordance, 20 % of samples were analyzed by both screening methods and validated by direct sequencing.

Statistical analysis

Genotype frequencies were calculated as the number of participants, with a particular genotype divided by the number of total participants. Tests for Hardy–Weinberg equilibrium among cases and controls were assessed using Pearson's Chi square test, with one degree of freedom, comparing expected genotype frequencies (based on observed qs) to observed genotype frequencies. Case–control differences on genotype frequencies were also assessed using Pearson's Chi square test.

The association between MBC risk and *SULT1A1* $Arg^{213}His$ (G>A) polymorphism was measured by the odds ratio (OR) and its corresponding 95 % confidence interval, by unconditional logistic regression, adjusted for age and center of enrollment. The analyses were performed with three separate logistic regression models based on dominant, recessive, and co-dominant effects (inheritance model). In the dominant model, the heterozygous variant and rare homozygous variant were combined in a dummy variable. In the recessive model, the variant was defined in a dummy variable as only the rare homozygous genotype. In the co-dominant model, both rare homozygous and heterozygous variant effects were estimated using two dummy variables.

Chi square test and logistic regression models were also performed in a case–case analysis, in order to evaluate the potential associations between *SULT1A1* $Arg^{213}His$ genotypes and specific MBC clinical–pathologic characteristics.

A P value < 0.05 was considered statistically significant. All the analyses were performed using SAS (SAS/STAT version 9.1) statistical program.

Results

All 1,180 samples, including 394 MBC cases and 786 male controls were genotyped for *SULT1A1* $Arg^{213}His$ (G>A) polymorphism. Genotype distribution was consistent with Hardy–Weinberg equilibrium ($P > 0.05$) among controls.

The distribution of genotype frequencies of the *SULT1A1* $Arg^{213}His$ polymorphism in MBC cases and controls, and the risk estimate, calculated by separate multivariate regression analyses, based on different transmission models (co-dominant, dominant, and recessive) are summarized in Table 1. Significant differences emerged in the distribution of genotypes between MBC cases and controls ($P < 0.0001$). The analysis of the genotype-specific risks by co-dominant model showed that individuals with A/A homozygous genotype (OR 3.09, 95 % CI 1.83–5.23; $P < 0.0001$) and individuals with G/A heterozygous genotype (OR 1.97, 95 % CI 1.50–2.59; $P < 0.0001$) were at increased MBC risk. These results were confirmed by dominant and recessive models (Table 1).

The associations of A/A and G/A genotypes with increased MBC risk persisted also, when 52 MBC carriers of germ-line *BRCA1/2* mutations were excluded from the analyses (Table 2).

Statistically significant association between *SULT1A1* risk genotypes and HER2 status emerged. No other significant associations were found (Table 3). In a case–case multivariate analysis adjusted for center of enrollment and age of patients, a statistically significant association between *SULT1A1* A/A risk genotype and HER2-positive tumors emerged (OR 4.70; 95 % CI 1.50–14.71; $P = 0.008$).

Table 1 Distribution of 394 MBC cases and 786 male population controls according to the *SULT1A1* Arg^{213}His (G>A) genotypes

Genotype	Cases		Controls		*P* value[a]	Co-dominant[b]		Dominant[b]		Recessive[b]	
	N	%	*N*	%		OR	95 % CI	OR	95 % CI	OR	95 % CI
G/G	154	39.1	436	55.5							
G/A	204	51.8	308	39.2		1.97	(1.50;2.59)	2.09	(1.60;2.73)		
A/A	36	9.1	42	5.3	**<0.0001**	3.09	(1.83;5.23)			2.22	(1.34;3.67)
Total	394		786			***P* < 0.0001**		***P* < 0.0001**		***P* = 0.002**	

[a] *P* value from Chi square test; *P* values < 0.05 in bold text

[b] Odds ratios (ORs) and 95 % confidence intervals (CI) according to co-dominant, dominant, and recessive models

Table 2 Distribution of 342 MBC cases not mutated in *BRCA1/2* genes and 786 male population controls according to the *SULT1A1* Arg^{213}His (G>A) genotypes

Genotype	Cases		Controls		*P* value[a]	Co-dominant[b]		Dominant[b]		Recessive[b]	
	N	%	*N*	%		OR	95 % CI	OR	95 % CI	OR	95 % CI
G/G	140	40.9	436	55.5							
G/A	172	50.3	308	39.2		1.84	(1.38;2.45)	1.95	(1.48;2.58)		
A/A	30	8.8	42	5.3		2.95	(1.69;5.13)			2.20	(1.29;3.75)
Total	342		786		**<0.0001**	***P* < 0.0001**		***P* < 0.0001**		***P* = 0.004**	

[a] *P* value from Chi square test; *P* values < 0.05 in bold text

[b] Odds ratios (ORs) and 95 % confidence intervals (CI) according to co-dominant, dominant, and recessive models

Table 3 Associations between *SULT1A1* Arg^{213}His (G>A) genotypes and clinical–pathologic features of MBC cases

Variable[a]		Total (%)	GG (%)	GA (%)	AA (%)	*P* value[b]
Breast/ovarian cancer family history	Positive	145 (36.8)	58 (40.0)	76 (52.4)	11 (7.6)	0.71
	Negative	249 (6.2)	96 (38.6)	128 (51.4)	25 (10.0)	
Personal history of other tumors	Positive	58 (15.2)	25 (43.1)	29 (50.0)	4 (6.9)	0.18
	Negative	324 (84.8)	125 (38.6)	170 (52.5)	29 (8.9)	
BRCA1/2 mutational status	Positive	52 (13.2)	14 (26.9)	32 (61.5)	6 (11.6)	0.18
	Negative	342 (86.8)	140 (40.9)	172 (50.3)	30 (8.8)	
ER	Positive	276 (91.7)	107 (38.8)	144 (52.2)	25 (9.0)	0.98
	Negative	25 (8.3)	10 (40.0)	13 (52.0)	2 (8.0)	
PR	Positive	250 (83.3)	97 (38.8)	132 (52.8)	21 (8.4)	0.90
	Negative	50 (16.7)	20 (40.0)	25 (50.0)	5 (10.0)	
HER2	Positive	59 (25.5)	24 (40.7)	25 (42.4)	10 (16.9)	**0.001**
	Negative	172 (74.5)	70 (40.7)	96 (55.8)	6 (3.5)	
MIB1	Positive	93 (44.9)	35 (37.6)	47 (50.5)	11 (11.9)	0.61
	Negative	114 (55.1)	43 (37.7)	62 (54.4)	9 (7.9)	
Lymph node	Positive	109 (42.1)	44 (40.4)	54 (49.5)	11 (10.1)	0.83
	Negative	150 (57.9)	56 (37.3	80 (53.9)	14 (9.4)	
Tumor grade	G3	89 (31.7)	33 (37.1)	48 (53.9)	8 (9.0)	0.95
	G1/G2	192 (68.3)	75 (39.1)	100 (52.1)	17 (8.8)	

[a] For some variables several data are missing

[b] *P* values from Chi square test; *P* values < 0.05 in bold text

Discussion

The primary aim of our study was to evaluate the possible influence of *SULT1A1* Arg^{213}His functional polymorphism on MBC risk by genotyping 394 MBC cases and 786 healthy male controls. Genotype frequencies of *SULT1A1* Arg^{213}His polymorphism were different between MBC cases and healthy male controls. The analyses of the genotype and allele-specific risks showed that in our series, males carrying the ^{213}His allele were at increased risk of

MBC. At present, there are no published data on the role of *SULT1A1* Arg^{213}His polymorphism in MBC; thus, our data are the first to demonstrate a possible association between a *SULT1A1* common functional polymorphism and BC susceptibility in men.

From an epidemiological point of view, MBC resembles post-menopausal ER-positive FBC with which it shares some major risk factors such as high estrogen levels [2, 3]. Association between the *SULT1A1* Arg^{213}His variant and BC risk has been investigated in women, but with inconclusive results [8–13]. The contrasting data in the literature concerning *SULT1A1* Arg^{213}His variant and FBC risk may reflect the heterogeneity of BC in women as well as the confounding factors related to the high disease frequency and high variability of hormone history found in women. Within this context, we propose that increased knowledge of the underlying mechanisms of MBC, unencumbered by these confounding factors, might be instrumental to a better understanding of the complex interrelationship between genetic, hormonal, and environmental factors involved in the pathogenesis of BC in both genders.

Recently, *SULT1A1* Arg^{213}His variant has been associated with increased risk of post-menopausal BC [17, 18]. Though more studies need to be conducted on this particular subgroup, our data seem to support these conclusions. Thus, results from our study may point to a common pathogenic mechanism involving alteration in the estrogen metabolic pathways that are present in both males and females.

Our results suggest that the role of *SULT1A1* Arg^{213}His as a genetic risk factor for MBC may be related to its function in estrogens metabolism. Men carrying the *SULT1A1* ^{213}His allele may be more susceptible to estrogen-induced carcinogenesis in mammary tissue due to the presence of high levels of bioactive estrogens. A high level of bioactive estrogens may provide a growth advantage for ER-positive tumors. Consistently, a high proportion of MBCs expresses hormone receptors. However, it cannot be excluded that the association between *SULT1A1* genotypes and BC risk could be even more complicated, considering the dual effect of SULT1A1 on both inactivation of estrogens and activation of environmental mammary carcinogens.

It is known that SULT1A1 participates in the elimination of 4-hydroxy-tamoxifen (4-OH-TAM), which is one of the major active metabolites of tamoxifen (TAM), and that functional genetic polymorphisms of *SULT1A1* may modify the pharmacokinetics of TAM therapy potentially influencing the activity of TAM [21]. TAM is generally considered the standard adjuvant treatment for hormone-dependent MBC [22]. Interestingly, several findings suggest that the possible reduction of SULT1A1 enzymatic activity could contribute to a minor elimination of estrogens on one hand, and an accumulation of active metabolites of TAM on the other [21, 23–25]. This paradoxical effect could increase estrogens' exposure through a competitive mechanism. In this context, MBC patients with *SULT1A1* His^{213}His genotype may benefit from hormone therapy that is different from TAM, such as aromatase inhibitors. However, prospective studies are needed to elucidate this speculation.

In this study, we also evaluated a possible association between *SULT1A1* Arg^{213}His genotypes and clinical–pathologic characteristics of MBCs. Results were statistically significant for an over-represented *SULT1A1* ^{213}His genotype in HER2-positive cases. Recently, we have shown that *BRCA2*-associated MBCs represent a subgroup of tumors with a peculiar phenotype characterized by HER2-positive status and aggressive behavior [19] and that *SULT1A1* gene deletion is significantly associated with *BRCA2*-related tumors [26]. Taken together, all these findings may suggest that the possible reduction of SULT1A1 enzymatic activity, due to either the presence of ^{213}His allele or of *SULT1A1* gene deletion, may contribute to an aggressive phenotype in MBC. This is consistent with the higher prevalence of lymph node metastases, which has been found in FBC patients with the *SULT1A1* Arg^{213}His polymorphism [10], again suggesting a possible common pathogenic mechanism in BC of both genders.

Although we studied a large sample size, a potential limitation of our study is that it is based on a series collected in a single country. Given the ethnic differences in the impact of *SULT1A1* Arg^{213}His polymorphism reported in BC risks among women from different populations [13, 14, 16, 17], further studies are needed to better define the role of *SULT1A1* Arg^{213}His polymorphism in MBC risk in additional populations.

In conclusion, our results indicate that *SULT1A1* Arg^{213}His variant could represent a low-penetrance risk factor for developing BC in men. Our study is the first to explore and demonstrate a possible association between this genetic polymorphism and MBC risk. Although further studies are needed to confirm these data, the national scope of our research may provide useful information for identifying males at increased risk of BC in Italy, and may serve to encourage additional MBC-related research nationally and internationally.

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Conflict of interest The authors declare that they have no conflict of interest.

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