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FREQUENCY OF GENETIC POLYMORPHISM IN GSTM1, GSTT1 AND GSTP1 GENES ASSOCIATED WITH BREAST CANCER IN WOMEN: A REVIEW

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Abstract: Genetic polymorphisms in genes related to the metabolism of xenobiotics, how the genes of the glutathione S-transferases superfamily (GSTM1, GSTT1 and GSTP1) have been associated with an increased risk for breast cancer (BC). A literature review was performed using the database *PubMed*, verifying the frequency of GSTM1, GSTT1 and GSTP1 polymorphisms in studies associated with breast cancer in the last decade, including 27 studies, 14 verified the frequency of GSTM1 and GSTT1 null polymorphisms in women without cancer and 22 in women with cancer; and for the GSTP1 gene, 12 studies verified the genotypic frequency of GSTP1 A/G in women without breast cancer and 18 in women with breast cancer. The mean frequency of the GSTT1 and GSTM1 null genes found in studies with women without breast cancer was 28% and 45% and the mean allele frequencies of the GSTP1 gene for women without breast cancer was 57.7% for the Ile allele and 34% for the Val allele, and the mean frequency of the GSTT1 and GSTM1 null genes found in studies with women with breast cancer was 34.7% and 41.4% and the mean allele frequencies of the GSTP1 gene for women with breast cancer was 59.8% for the Ile allele and 40.2% for the Val allele. Therefore, considering the importance of these genes in carcinogen metabolism, together with the allelic and genotypic frequencies of the polymorphisms studied in this review that differ from one study to another, we suggest that other factors may influence this distribution.

Keywords: Genetic polymorphisms, GSTM1, GSTT1, GSTP1, Breast Cancer.

INTRODUCTION

Breast cancer (BC) is the second most common type of cancer in the world, second only to lung cancer, and the first type of cancer in women, affecting all age groups. With

life expectancy increasing worldwide, the increased incidence of non-communicable diseases, including breast cancer, has gained a prominent place in world epidemiology¹.

The causes of CM can be hereditary, a consequence of mutations in genes related to the germline (high penetrance genes), or they can be associated with polymorphisms in low penetrance genes².

Genes involved in carcinogen metabolism can be used as markers of individual susceptibility to cancer and their products, detoxifying enzymes, can exacerbate or suppress xenobiotic activity³. Thus, changes in the balance between activation and detoxification of carcinogens may explain individual variations in response to exposure to these agents⁴. Among the genes that are distinguished by their possible role in detoxification are those of the glutathione S-transferases (GST) family of enzymes involved in phase II of biotransformation, acting on carcinogens, environmental pollutants, drugs and other xenobiotics⁵.

The three main genes of the glutathione S-transferase family are GSTM1, GSTT1 and GSTP1. The GSTM1 gene is located on chromosome 1p13.3, and 20% to 50% of the population has a homozygous deletion, not expressing the enzyme^{6,7}. The GSTT1 gene is located on chromosome 22q11.2, and it is also polymorphic in the population, with null allele frequencies ranging between 20 and 60% in different human populations⁸. The GSTP1 gene is located on chromosome 11q13, and the presence of a polymorphism at codon 105 (substitution of isoleucine to valine, rs1695) appears to result in reduced activity of the GSTP1 enzyme⁹.

The GSTM1 and GSTT1 null and GSTP1 II and 105Val polymorphisms have been associated with increased susceptibility to various forms of cancer. The characterization of populations regarding the frequency of

genetic polymorphisms related to CM and are fundamental tools to establish strategies for the prevention and treatment of the disease.

GOAL

To verify the frequency of GSTM1, GSTT1 and GSTP1 polymorphisms in studies associated with breast cancer, also verifying if they were in Hardy-Weinberg Equilibrium (HW).

MATERIALS AND METHODS

The present study is a literature review, using the PubMed database (National Library of Medicine, using the following descriptors: Breast Cancer, Glutathione-S-transferase, Polymorphisms, GSTM1, GSTT1 and GSTP1, as well as the combination between them. Articles that reported an association between GSTM1, GSTT1 and GSTP1 with breast cancer in the period from 2005 to 2015 were included in the study.

RESULTS

25 studies were included, 13 of which verified the frequency of GSTM1 and GSTT1 null polymorphisms in women without cancer and 21 in women with cancer; and for the GSTP1 gene, 12 studies verified the genotypic frequency of GSTP1 A/G in women without breast cancer and 17 in women with breast cancer. Results represented in tables (1, 2, 3 and 4).

The minimum, average and maximum frequencies of GSTT1 and GSTM1 null genes found in studies with women without breast cancer were (10%, 28%, 48%) and (30%, 45%, 45%) and allele frequencies minimum, mean and maximum of the GSTP1 gene for women without breast cancer was (20%, 57.7%, 80%) for the Ile allele and (20%, 34%, 80%) for the Val allele, and the minimum, average and maximum frequency of null GSTT1 and GSTM1 genes found in studies with women

with breast cancer was (13%, 34.7%, 79.6%) and (19.7%, 41.4%, 63.5%) and the minimum, average and maximum allele frequencies of the GSTP1 gene for women with breast cancer were (5%, 59.8%, 74%) for the Ile allele and (26%, 40.2%, 95%) for the Val allele.

DISCUSSION

The average frequency of null GSTT1 and GSTM1 genes found in studies with women without breast cancer was 28% and 45%, respectively, among the studies by Chirilă et al¹⁴. found a frequency of 10% for the GSTT1 gene, and that of Kaushal et al.³⁰ had a frequency of 29.9% for the GSTM1 gene, these being the lowest frequencies found. Unlike Pongtheerat et al²⁰. who observed a frequency of 48.2% for the GSTT1 gene and Torresan et al¹¹. who observed a frequency of 55% for the GSTM1 gene, these being the highest frequencies found in studies with women without breast cancer.

The mean allele frequencies of the GSTP1 gene for women without breast cancer were 57.7% for the Ile allele and 34% for the Val allele, and among the studies, Sohail et al²⁵. observed a frequency of 20% for the Ile allele and 80% for the Val allele. The study by Kaushal et al³⁰. observed a frequency of 80% for the Ile allele and 20% for the Val allele.

In parallel, the average frequency of null GSTT1 and GSTM1 genes found in studies with women with breast cancer was 34.7% and 41.4%, respectively, among studies, the one by Jaramillo-Rangel et al¹². found the frequency of 13.2% for the GSTT1 gene, and that of Romero et al¹⁷. had a frequency of 18.9% for the GSTM1 gene, these being the lowest frequencies found. Unlike Duggan et al²⁴. who observed a frequency of 79.6% for the GSTT1 gene and Ramalhinho et al²⁸. who observed a frequency of 63.5% for the GSTM1 gene, these being the highest frequencies in women with breast cancer.

The mean allele frequencies of the GSTP1 gene for women with breast cancer were 59.8% for the Ile allele and 40.2% for the Val allele, and among the studies, Sohail et al²⁵. observed a frequency of 5% for the Ile allele and 95% for the Val allele and the studies by Kaushal et al³⁰. and Syamala et al³⁹. observed frequencies of 74% for the Ile allele and 26% for the Val allele.

CONCLUSION

In this review, the allelic and genotypic frequencies of the studied polymorphisms differ from one study to another, showing that other factors can influence this distribution, as well as epigenetic mechanisms. Hence the importance of epidemiological and genetic studies that assess environmental carcinogens contributing to this increase and that genetic differences in their metabolism may be those associated with individual variations in susceptibility to breast cancer.

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References	Country	number	Genotypic frequencies	
			GSTT1 (-) n (%)	GSTM1 (-) n (%)
Jaramillo-Rangel <i>et al.</i> 2015	Mexico	113	22(19,5%)	34(30,1%)
Chirilă <i>et al.</i> 2014	Romania	40	4(10,0%)	17(42,5%)
Sohail <i>et al.</i> 2013	Pakistan	102	16(32,0%)	22(45,0%)
Gonçalves <i>et al.</i> 2013	Brazil	49	19(38,3%)	21(43,3%)
Aguiar <i>et al.</i> 2012	Brazil	750	158(21,0%)	339(45,2%)
Martínez-Ramírez <i>et al.</i> 2012	Mexico	150	42(28,0%)	61(41,3%)
Ramalhinho <i>et al.</i> 2011	Portugal	102	18(17,6%)	41(40,2)
Kaushal <i>et al.</i> 2010	India	174	69(39,7%)	52(29,9%)
Anton <i>et al.</i> 2010	Brazil	30	11(36,7%)	13(43,3%)
Pongtheerat <i>et al.</i> 2009	Thailand	56	27(48,2%)	24(42,9%)
Morais <i>et al.</i> 2008	Brazil	169	33(19,5%)	75(44,4%)
Torresan <i>et al.</i> 2008	Brazil	102	33(30,0%)	56(55,0%)
Kvitko <i>et al.</i> 2006	Brazil	190	49(25,7%)	84(44,2%)
(-) null				

Table 1. GSTT1 (-) and GSTM1 (-) polymorphisms in breast cancer-unaffected in women

References	Country	n	Frequências genotípicas	
			GSTT1 (-) n (%)	GSTM1 (-) n (%)
Jaramillo-Rangel <i>et al.</i> 2015	Mexico	243	32(13,2%)	118(48,6)
Zhou <i>et al.</i> 2015	China	420	194(46,2%)	209(49,8%)
Aiste <i>et al.</i> 2015	Lithuania	80	14(17,5%)	39(48,8%)
Chirilă <i>et al.</i> 2014	Romania	60	14(23,7%)	35(59,3%)
Liu <i>et al.</i> 2014	China	382	215(56,3%)	154(40,3%)
Duggan <i>et al.</i> 2013	USA	533	424(79,6%)	280(52,5%)
Sohail <i>et al.</i> 2013	Pakistão	49	13(27,0%)	21(43,0%)
Gonçalves <i>et al.</i> 2013	Brazil	49	30(61,7%)	28(58,8%)
Yun-Lu Bai <i>et al.</i> 2012	China	159	74(46,5%)	35(22,0%)
Romero <i>et al.</i> 2012	Spain	159	74(46,5%)	30(18,9%)
Martínez-Ramírez <i>et al.</i> 2012	Mexico	150	47(31,3%)	65(43,3%)
Ramalhinho <i>et al.</i> 2011	Portugal	102	37(43,5%)	54(63,5%)
Lourenço <i>et al.</i> 2010	Brazil	87	16(18,4%)	33(37,9%)
Gor <i>et al.</i> 2010	USA	350	61(17,4%)	184(52,6%)
Henningsom <i>et al.</i> 2010	Sweden	253	43(17,0%)	140(55,3%)
Kaushal <i>et al.</i> 2010	India	117	33(28,2%)	23(19,7%)
Pongtheerat <i>et al.</i> 2009	Thailand	40	18(45,0%)	14(35,0%)
Morais LMTS <i>et al.</i> 2008	Brazil	91	20(15,0%)	40(35,0%)
Syamala <i>et al.</i> 2007	India	347	56(16,0%)	119(34,3%)
Samson <i>et al.</i> 2007	India	250		65(26,0%)

(-) null

Table 2. GSTT1 (-), GSTM1 (-) polymorphisms in women with breast cancer

References	Country	n	genotypic frequencies			Allelic Frequencies		
			II - number (%)	IV - number (%)	VV - number (%)	I(%)	V (%)	*HW
Jaramillo-Rangel <i>et al.</i> 2015	Mexico	118	35(29,7%)	53(44,9%)	30(25,4%)	0.52	0.48	1,18
Chirilă <i>et al.</i> 2014	Romania	40	21(53,8%)	17(43,5%)	1(2,5%)	0.76	0.24	1,19
Sohail <i>et al.</i> 2013	Pakistan	43	3(7,0%)	14(28,0%)	33(67,0%)	0.20	0.80	2,05
Aguiar <i>et al.</i> 2012	Brazil	750	330(44,0%)	329(43,9%)	91(12,1%)	0.66	0.34	0,42
Saxena <i>et al.</i> 2012	India	215	101(47,0%)	75(34,9%)	39(18,1%)	0.64	0.36	12,2
Martínez-Ramírez <i>et al.</i> 2012	Mexico	150	43(32,0%)	66(48,6%)	41(19,3%)	0.51	0.49	2,17
Ramalhinho <i>et al.</i> 2011	Portugal	102	48(47,1%)	54(52,9%)				
Kaushal <i>et al.</i> 2010	India	174	108(62,1%)	62(35,6%)	4(2,3%)	0.80	0.20	2,08
Torresan <i>et al.</i> 2008	Brazil	102	61(59,0%)	38(37,0%)	3(4,0%)	0.78	0.22	1,03
Syamala <i>et al.</i> 2007	India	250	125(50,0%)	109(43,6%)	16(6,4%)	0.72	0.28	1,49
Samson <i>et al.</i> 2007	India	500	230(46,0%)	219(43,8%)	51(10,2%)	0.68	0.32	0,02
Kvitiko <i>et al.</i> 2006	Brazil	190	76(40,0%)	94(49,5%)	20(10,5%)	0.65	0.35	1,35

*HW – Equilibrio de Hardy-Weinber < 3,84 para p < 0,05

Table 3. GSTP1 polymorphism (Ile105Val) in women without breast cancer

Table 3. GSTP1 (Ile105Val) polymorphism in breast cancer-unaffected in women

Referências	País	n	Frequências genotípicas			Frequências Alélicas		*HW
			II - n (%)	IV - n (%)	VV - n (%)	I (%)	V (%)	
Jaramillo-Rangel <i>et al.</i> 2015	Mexico	242	58(24,0%)	105(43,4%)	79(32,6%)	0.46	0.54	3,84
Siddiqui Islam <i>et al.</i> 2015	Bangladesh	256	131(51,2%)	98(38,3%)	27(10,5%)	0.7	0.30	1,77
Zhou <i>et al.</i> 2015	China	420	178(42,4%)	174(41,4%)	68(16,2%)	0.63	0.37	5,11
Aiste <i>et al.</i> 2015	Lithuania	80	42(52,5%)	28(35%)	10(12,5%)	0.70	0.30	2,22
Liu <i>et al.</i> 2014	China	382	150(39,3%)	154(40,3%)	78(20,4%)	0.59	0.41	10,28
Chirilă <i>et al.</i> 2014	Romania	58	29(49,1%)	26(44,0%)	3(5,0%)	0.72	0.28	0,86
Duggan <i>et al.</i> 2013	USA	533	223(41,8%)	250(46,9%)	60(11,3%)	0.65	0.35	0,68
Sohail <i>et al.</i> 2013	Pakistan	50	0	5(10,0%)	45(90,0%)	0.05	0.95	0,14
Yun-Lu Bai <i>et al.</i> 2012	China	159	81(50,9%)	35(22,0%)	43(27,0%)	0.62	0.38	45,23
Saxena <i>et al.</i> 2012	India	215	81(37,7%)	89(41,4%)	45(20,9%)	0.58	0.42	4,73
Romero <i>et al.</i> 2012	Spain	159	65(40,9%)	75(47,2%)	19(11,9%)	0.64	0.36	0,17
Martínez-Ramírez <i>et al.</i> 2012	Mexico	150	40(27,3%)	39(34,6%)	71(38,0%)	0.40	0.60	31,14
Ramalhinho <i>et al.</i> 2011	Portugal	102	39(45,9%)	46(54,1%)				
Henningsson <i>et al.</i> 2010	Sweden	253	114(45,1%)	117(46,2)	22(8,7%)	0.68	0.32	1,11
Kaushal <i>et al.</i> 2010	India	117	62(53,0%)	48(41,0%)	7(6,0%)	0.74	0.26	0,37
Syamala <i>et al.</i> 2007	India	125	72(57,6%)	42(33,6%)	11(8,8%)	0.74	0.26	1,73
Samson <i>et al.</i> 2007	India	250	116(46,6)	105(41,9)	29(11,5%)	0.67	0.33	0,52

HW – Equilibrio de Hardy-Weinber < 3,84 para p < 0,05

Tabela 4. Polimorfismo GSTP1 (Ile105Val) em mulheres com câncer de mama

Table 4. GSTP1 (Ile105Val) polymorphism in women with breast cancer