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Polymorphism of Glutathione-S -Transferase P1 gene in Breast Cancer patients in Baghdad /Iraq

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Abstract:

Glutathion S-transferase enzymes are detoxifying enzymes – phase II enzymes, which play an important role in protecting cells from damage caused by endogenous and exogenous compounds and subsequently, are crucial in protecting the DNA. The aim of this study is to evaluate polymorphism of Glutathion S-transferase P1 (GSTP1) in Iraqi women breast cancer. Blood samples were collected from 65 Iraqi women diagnosed as breast cancer patients who attended to Oncology Teaching Hospital and Al-Yarmouk Teaching Hospital. In addition to 59 healthy women as control group. Genomic DNA was extracted then genotyping was performed by restriction fragment length polymorphism- polymerase chain reaction (RFLP-PCR) for GSTP1 gene. The frequencies of GSTP1 polymorphism (Ile105Val) in the breast cancer group were: 41.54% for wild type (Ile/Ile), 49.23% for heterozygote (Ile/Val) and 9.23% for homozygote mutant (Val/Val), while in control group was 57.63 for wild (Ile/Ile), 42.37(Ile/Val) heterozygote and 0.00 %(Val/Val) homozygote. The results show there were statistically significant differences in the distribution of (Val/Val) genotype and Val allele between patients and controls groups ($p<0.05$), (OR= 16.3091; 95% CI= 0.8798 to 302.3326) and (OR= 1.9380; 95% CI= 1.0274 to 3.6556) respectively . This study showed that GSTP1 (Val/ Val) genotype may be associated with an increased risk for breast cancer among Iraqi women.

Keywords: *glutathione S-transferase; breast cancer ; GSTP1; restriction fragment length polymorphism*

Introduction:

Breast cancer is the most common type of cancer that affects females (1). The interplay between genetic and epigenetic events, as well as environmental risk factors, has significant implications in the pathogenesis of breast cancers (2). Some researchers are concerned with identifying new genetic, epigen¬etic, prognostic and predictive factors. It has been shown that genetic factors (mutations in BRCA1 and BRCA 2) and reproduc-tive history account for one-third of all breast cancer cases. However, in two-thirds of breast cancer cases the etiology remains unclear. Previous epidemiological studies have indi¬cated that certain environmental agents may play an important role in the development of breast carcinomas (3). Thus, the capacity to metabolize and detoxify exogenous toxins may correlate with an individual's susceptibility to environment-induced breast cancer (2).It has been postulated that polymorphisms in genes involved in DNA repair, carcinogen metabolism and growth factor receptors increase the risk of cancer in some individuals (4).Glutathione S-transferases are major phase II detoxifying enzymes (5),detoxify a broad range of electrophilic compounds including carcinogens, chemotherapeutics, pharmaceuticals, pesticides, herbicides, industrial chemicals and pollutants, products of oxidative damage and natural plant toxins (6), through conjugated them to glutathione to form their corresponding glutathionyl conjugates, which often results in less reactive and more water-soluble compounds. This minimizes the potential of damage from xenobiotics and eliminates these compounds from the body. Glutathione S-transferases can protect against macromolecules such as protein, nucleic acid and lipids oxidized by reactive oxygen species (ROS), regeneration of S-thiolated proteins, detoxification of products of lipid peroxidation and biosynthesis of physiologically important metabolites. Moreover, a number of endogenous compounds such as prostaglandins and steroids are metabolized via glutathione conjugation (7).

Glutathione –S- transferase P1 is involved in the detoxification of base propenals an metabolizes carcinogenic products such as benzo-(α)-pyrene dial epoxide, and acrolein, which are derived from cigarette smoke (8). Biochemical studies indicated that GSTP1 Val105 allele has a lower thermal stability than GSTP1 Ile105 allele, and Val homozygotes had a lower

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conjugating activity than Ile homozygotes, with heterozygotes displaying intermediate activity. Individuals with at least one Val allele at codon105 of GSTP1 enzyme don't have ability to break down both chemotherapeutics and the carcinogen found in cigarettes. It was therefore claimed that variation in carcinogen breakdown among individuals forms a foundation for cancer development within humans (9, 10) and might have an underlying predisposition to cancer when exposed to environmentally derived or endogenously formed GSTP1 substrates . Indeed, the GSTP1 codon 105Val allele was associated with a significantly increased risk of lung, bladder, testicular cancer and breast cancer (8). This is the first study to our knowledge in Iraq, to give the genotype frequency of GSTP1 gene and its association with breast cancer in Iraqi women. There are little knowledge about causes of breast cancer in Iraqi women. Hence the present study was under taken to determine the distribution genotype frequencies for GSTP1(Ile105Val) among patients with breast cancer and controls, and to look for association of the polymorphisms with the risk of breast cancer.

Materials and Methods:

Specimens:

The study group included a total of 124 subjects comprising 65 women with invasive ductal carcinoma and 59 healthy individuals were selected to serve as control group. Samples were collected from Oncology Teaching Hospital and Al-Yarmouk Teaching Hospital in Baghdad– Iraq, between June to September 2014. Five mL of blood were collected into EDTA tube from both cases and controls . DNA was extracted using genomic DNA extraction kit (Bionear, Korea). The products of DNA extraction were verified by horizontal electrophoresis in 1% agarose. DNA concentrations were determined using Nanodrop and DNA quality was determined by gel electrophoresis of extracted products.

Genotyping of GSTP1 polymorphism (Ile105Val)

Genomic DNA was used to amplify 176-bp fragment using specific primer sequences: forward primer (F-5-ACCCCAGGGCTCTATGGGAA-3) and reverse primer (R-5-TGAGGGCACAAGAAGCCCCT-3) according to Korytina et al., 2005(11). The PCR reaction mixture was 25 µL consisted of approximately 100–150 ng of genomic DNA, 0.6 µL (10 pmol/L) of each primer, 12.5 µL of Hotstart green Master Mix (promega) and 6.3 µL of free DNAase distilled water. The PCR cycling conditions include: initial denaturation was carried out for 5 min. at 95 0C followed by 30 cycles at 94 0C for 30 s. ,Annealing at 60 0C for 30 s, then extension at 72 0C for 30 s, and final extension was done at 720C for 10 min. After amplification, 10 µL of PCR products were subjected to restriction digestion using of 5 U of BsmA1 restriction enzyme (England biolab) for 2 hours.

Statistical analysis

The Pearson $\chi 2$ criterion ($p < 0.05$), odds ratios (OR) and 95% confidence intervals (CI) tests were used to compare the frequencies of polymorphisms of GSTP1 between the two groups, using the SASS program.

Results:

Table 1 shows the distribution of selected demographic characteristics and known major risk factors for breast cancer. Family history of breast cancer was also found to be significantly different (P <0.0001) in breast cancer cases when compared to control, there were (33.85%) of the patients women had positive history of breast cancer in their families . The results indicated that women with positive history of breast cancer were more susceptible to breast cancer when compared to others don't have family history of breast cancer .(table 1).

However, other factors such as number of pregnancies, age at first pregnancy, breastfeeding, use of oral contraceptive, smoking, marital status, were not associated with risk of breast cancer (table1).

Table 1: Demographic characteristics of the females with breast cancer and female controls.

Risk factor		Breast cancer N= 65	Controls N= 59	P (value)	Chi-square ($\chi 2$)
Number of pregnancies	Mean ± SD	2.35 ± 4.4	2.48 ± 2.6	* 0.0245	---
Age at first pregnancy in years	Mean ± SD	5.12 ± 23.4	1.70 ± 22.25	NS 0.672	---
Breastfeeding	Yes	(79.66%) 47	(% 82.5) 33	0.724855	0.1239
	No	(20.34%) 12	(17.5%) 7		
Use of oral contraceptive	Yes	(% 49.15) 29	(62.5%) 25	0.190606	1.7129
	No	(50.85%) 30	(37.5%) 15		
Smoking	Yes	(3.08%) 2	(0.00%) 0	0.497115PFE	
	No	(96.92%) 63	(100.0%) 59		
Family history of breast Cancer	Yes	(33.85%) 22	(3.39%) 2	0.0001> PFE	
	No	(66.15%) 43	(96.61%) 57		
Marital status	Single	(9.23%) 6	(32.20%) 19	0.001451	10.1399
	Married	(90.77%) 59	(67.80%) 40		

* (P≤0.05), NS: Non-significant. ,PFE: Probability by fisher exact test

The DNA was extracted from lymphocyte of patients with breast cancer and healthy controls to study the polymorphism of GSTP1 gene by RFLP-PCR , between these two groups. A fragment containing A313 G polymorphism in exon 5 of GSTP1gene was amplified as 176 bp band, Figure (1 -A). For detection of this polymorphism ,BsmAI restriction enzyme was used to produce one band at 176bp in Homozygous wild type (Ile/Ile), 3bands at 176 bp,91bp, and 85bp in Heterozygous mutant(Ile/Val) and two bands at 91bpand 85bp in Homozygous mutant(Val/Val) as shown in Figure (1-B).

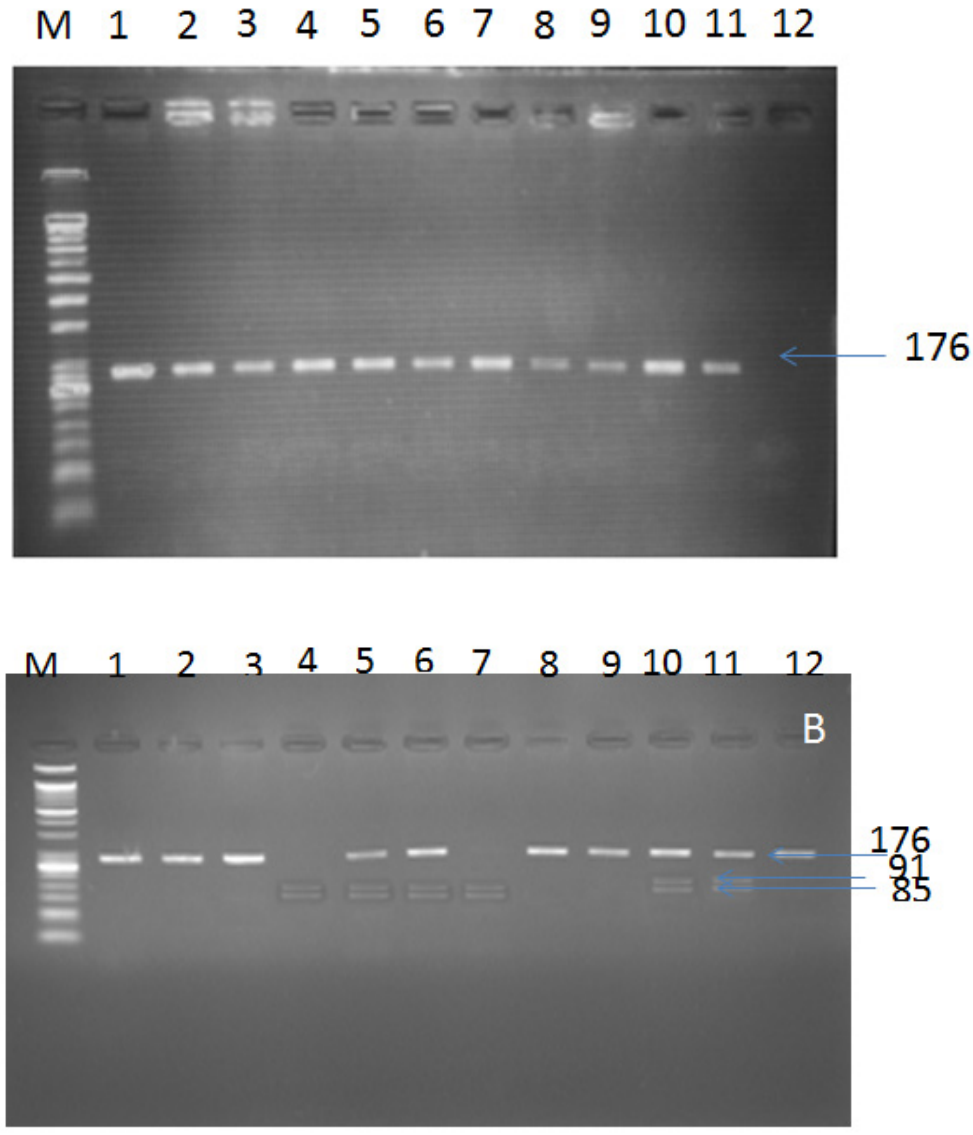

Figure (1):A, Electrophoresis of PCR product for GSTP1 gene on 2% agarose gel. M:DNA molecular weight marker 25bp,lane (1-11)represent PCR products for GSTP1 gene, lane 12 represent negative control .B, PCR-RFLP analysis of GSTP1 gene polymorphism using BsmAI restriction enzyme :M:DNA molecular weight marker 25bp. Lane (1,2,3,8,9,12)represent Homozygous wild type (Ile/Ile),;lane (5,6,10,11) represent Heterozygous mutant (Ile/Val),lane (4,7)represent Homozygous mutant (Val /Val)

The frequencies of GSTP1 polymorphism (Ile105Val) in the breast cancer group were: 41.54% for wild (Ile/Ile), 49.23% (Ile/Val) heterozygote and 9.23% (Val /Val) homozygote, while in the control group the frequencies of GSTP1 polymorphisms was 57.63 % wild (Ile/Ile), 42.37% (Ile/Val) heterozygote and 0.00% (Val/Val) homozygote. There were statistically significant differences between patients and control group for (Val/Val) genotype as well as for Val allele ($p<0.05$), the value of odds ratio (OR) for the (Val /Val) genotype was equal to (16.3) this finding indicated that GSTP1 (Val/ Val) genotype was associated with an increased risk for breast cancer. Furthermore small significant differences was observed for the (Ile/Val + Val/Val) genotype (P =0.07) while, no statistically significant differences were observed regarding the (Ile/Val) genotype (P> 0.05). All these results summarized in (table 2) .

Table 2: Genotype distribution and allele frequency of GSTP1 gene in breast cancer and controls.

Genotypes/alleles	Cases (%) n N= 65	Controls (%) n N=59	OR with 95% CI	Chi-square ($\chi 2$)	p-value
Ile/Ile	(41.54) 27	(57.63) 34	Reference	-	-
Ile/Val	(49.23) 32	(42.37) 25	(to 3.3357 0.7789)1.6119	1.6629	0.1983
Val /Val	(9.23) 6	(0.00) 0	(to 302.3326 0.8798)16.3091	(9.23) 6	PFE 0.0110
Ile/Val+ Val/Val	(58.46) 38	(42.37) 25	(to 3.9095 0.9371) 1.9141	3.203	0.0748
Ileu allele	66.15%	78.81%	(to 3.6556 1.0274)1.9380	4.2382	0.0395
Val allele	33.85%	21.19%			

OR: odd ratio, CI: Confidence Interval , PFE: Probability by Fisher's exact test

The results in this study demonstrated there is nonsignificanse differences between GSTP1 genotype and parameters (age, affected site, breast feeding, marital status, Family history and Smoking) in patients with breast cancer (table 3).

Table 2: Genotype distribution and allele frequency of GSTP1 gene in breast cancer and controls.

Parameters		GSTP1 genotype		
		Ile/Ile N(%)	Ile/Val N(%)	Val /Val N(%)
Age	Premenapousal (21.53) 14	6(42.86)	7(50.00)	1(7.14)
	Menapousal (52.31) 34	16(47.06)	15(44.12)	3(8.82)
	Postmenapousal (26.15) 17	5(29.41)	10(58.82)	2(11.77)
Affected site	Right 26 (40.00)	9(34.61)	15(57.69)	2(7.69)
	Left 39 (60.00)	18(46.15)	17(43.59)	4(10.26)
Breast feeding	Yes 47 (79.6)	21(44.68)	21(44.68)	5(10.64)
	No 12(20.4)	(50.00)6	6(50.00)	0(0.00)
Marital status	Single =6(9.23)	27(45.76)	27(45.76)	5(8.48)
	Married 59(90.77)	0 (0.00)	5(83.33)	1(16.67)
Family history	Yes 22(33.85)	11(50.00)	10(45.45)	1(4.55)
	No 43(66.15)	16(37.21)	22(51.16)	5(11.63)
Smoking	Yes 2(3.08)	1(50.0)	1(50.0)	0(0.00)
	No 63 (96.98)	26 (41.27)	31 (49.21	6 (9.52)

Discussion:

Variation or deletion of GST enzyme activity in individuals results in impaired removal of DNA damaging electrophiles, which leads to increased risk of somatic mutation leading to tumor formation (12).

GSTP1 was the first isoenzyme shown to inhibit the c-Jun NH2-terminal kinase (JNK) complex and to play a role in the damage induced by reactive oxygen species due to oxidative or chemical stress (13). In our study, significant elevation in the frequency of GSTP1 (Val/Val) genotype and Val allele was observed in breast cancer group as compared to control group($p<0.05$). The results of genotype (Table 2) may confer risk to develop breast cancer and these results were in agreement with Balmukhanov et al., 2013 (14), Sohail et al., 2013 (15) Lu et al., 2011 (16), and in consist with other studies by Hashemi et al., 2012 (17), and Rodriguez et al., 2014 (18).

(Val/Val) genotype is known to be associated with defective detoxification of base propanols that arise from DNA oxidation thus interfering with cellular protection against oxidative stress. Several studies had also reported significant association of valine allele with susceptibility to develop tumors of bladder, lung, multiple myeloma, chronic myeloid leukemia (19-23). The GSTP1 enzyme is involved in the metabolism of various drugs used in chemotherapy and several studies were carried out to measure the activities of enzymes as a factor for drug resistance in tumor cells (15). Ge et al., 2013 (24) found that patients with GSTP1 105Val genotype had a better disease free survival after cyclophosphamide (CTX)- based chemotherapy than those with Ile/Ile. The study has investigated possible correlation between GSTP1 polymorphism and some risk factors included (age, affected site, breast feeding, marital status, family history, and smoking) among breast cancer patients. There is non significance differences between all these factors and GSTP1 genotype. Ge et al., 2013 (24) found that GSTP1 (Ileu105Val) genotype significantly increased with age of patients >= 50 years, while Gudmundsdottir et al.,2001(25) reported in their research ,there was non significant association between (GSTM1,GSTT1,GSTP1) and age. As well as Sohil et al., 2013(15) reported non significant differences between polymorphism of GSTP1 and smoking in patients with breast cancer .

Helzlsouer et al., 1998 (20) found that family history and smoking were significantly associated with the development of breast cancer, which is consistent with the fact that genetic factors along with environmental ones might be playing a role in breast cancer development. The involvement of GST enzymes in detoxification of xenobiotics is a well-established phenomenon therefore further studies on gene- environment (specifically smoking or pesticides exposure) interactions in relation to breast cancer could provide a valuable insight into the disease and a point to environment modification for disease prevention . Egan et al., 2004 (26) suggested that the risk of cancer due to GST family depends on the genetic background or the environmental factors such as smoking or estrogen level. The estrogen level is greatly lower in Asian women therefore the environmental carcinogens especially metabolized by GSTP1could greatly contribute to breast cancer development in populations with low estrogen exposure. In conclusion, Val/Val genotype might be considered as risk genotype for developing of breast cancer in Bagdad city .

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التنميط الوراثي لجين GSTP1 في مرضى سرطان الثدي لمحافظة بغداد/ العراق

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الخلاصه:

انزيمات الكلوتاثيون S-ترانسفيراز هي الانزيمات المسؤلة عن ازالة السموم –(انزيمات الطور الثاني) و التي تلعب دورا مهما في حماية الخلايا من الضرر الذي تسببه المركبات الداخلية والخارجية. فهي بذلك، تشكل عاملا حاسما في حماية الحامض النووي.

جمعت عينات دم من 65 امرأة عراقية شخصوا على أنهن مريضات بسرطان الثدي من مراجعات مستشفى الأورام التعليمي ومستشفى آليرموك التعليمي بالإضافة إلى 59 امرأة يتمتعن بصحة جيدة كمجموعة تحكم. استخلص الحامض النووي ثم تم إجري التنميط الجيني بتقنية RFLP-PCR لجين GSTP1. وشكلت ترددات الانماط المتعددة(Ile105Val) لجين GSTP1 في مجموعة سرطان الثدي و 41.54٪ للنمط الجيني القياسي (Ile /Ile) و 49.23٪ للنمط المتغاير (Val / Ile) و 9.23٪ للنمط الجيني الطافر متماثل الاليل (Val / Val) ، بينما في المجموعة الضابطة شكلت ترددات الانماط نسب مقدارها 57.63 للنمط الجيني القياسي (Ile /Ile) و 42.37 (Val / Ile) للنمط المتغاير و0.00٪ (Val / Val) للنمط الجيني الطافر متماثل الاليل. أظهرت النتائج وجود فروق ذات دلالة إحصائية في توزيع السيطرة النمط الجيني (Val/Val) والاليل Valبين المرضى ومجموعة التحكم الاصحاء ;p<0.05, (OR= 16.3091 (95% CI= 0.8798 to 302.3326

(OR= 1.9380; 95% CI= 1.0274 to 3.6556),على التوالي. وأظهرت هذه الدراسة أن النمط الجيني (Val / Val) لجين GSTP1 مرتبط بزيادة الاصابة بسرطان الثدي بين النساء العراقيات .