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Associations between hypoxia-inducible factor-1α (HIF-1α) gene polymorphisms and risk of developing breast cancer

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The C1772T, G1790A and C111A polymorphisms of Hypoxia-inducible factor-1α (HIF-1α) gene were analyzed in a hospital-based Malaysian population using PCR-RFLP method. Genomic DNA was extracted from the blood samples collected from 410 breast cancer patients and 275 normal and healthy women. We investigated the association between HIF-1α polymorphisms and breast cancer risk, and clinico-pathological parameters in the population. The genotype and allele frequencies of C1772T (P=0.0093 vs P=0.0024) polymorphism were significantly different between the breast cancer cases and normal subjects but similar association was not observed for G1790A (P>0.05) and C111A (P>0.05) polymorphisms, respectively. Women who were CT heterozygotes (OR=1.51; 95% CI, 1.01-2.25), TT homozygotes (OR=4.03; 95% CI, 1.09-17.60) and carriers of T allele genotype (OR=1.65; 95% CI, 1.13-2.43) were significantly associated with increased risk of breast cancer. Significant relationship was observed also between T allele and breast cancer risk (OR=1.69; 95% CI, 1.20-2.40). Clinico-pathological analysis showed that 1772T allele genotype was significantly associated with nodal metastases (P=0.0478) but independent of ER status, tumor grade and patients' age (P>0.05). Our observations suggest that the polymorphic allele of C1772T may be associated with increased risk of developing breast cancer, and presence of 1772T allele may be a useful genetic marker for tumor prognosis.

Keywords. Hypoxia-inducible factor-1α, genetic polymorphism, breast cancer.

Hypoxia-inducible factor-1 (HIF-1), consists of an α and a β subunit, is a heterodimeric basic helix-loop-helix transcription factor and a key regulator of cellular response to hypoxia [1]. The HIF-1α subunit determines the transcriptional activity of HIF-1, and the expression levels of HIF-1α is tightly regulated in response to oxygen levels [1, 2]. The subunit is hydroxylated and degraded rapidly under normoxia but it becomes stabilized or even induced in response to hypoxia conditions [1]. The gene has been shown to play an important role in carcinogenesis, tumor progression and metastases through activation of several genes associated in angiogenesis, cell survival, proliferation, erythropoiesis, energy metabolism and invasion [2–5]. Under the reduced oxygen pressure, HIF-1α regulates the expression of several genes such as vascular endothelial growth factor (VEGF) and genes linked with glycolytic pathway [6]. Furthermore, under hypoxic conditions, degradation of HIF-1α protein is suppressed and the protein is rapidly accumulated in the cell [1, 2].

Increased expression of HIF-1α was observed in several cancers including head and neck, breast, prostate, kidney, non-small cell lung, endometrial, colon, esophagus, pancreas and stomach cancers [2, 7–10]. A significant association between overexpression of the HIF-1α and mortality has been reported for many cancer types [2]. Overexpression of HIF-1α was demonstrated in primary as well as metastatic breast carcinomas [7, 11]. Upregulation of HIF-1α has been detected in both HER2 and ER positive and negative tumors [7, 12]. Elevated levels of HIF-1α has been associated with poorer outcome regardless of ER status [7, 11, 12]. High levels of HIF-1α was also associated with proliferative markers such as Ki-67 and cyclin A expression levels [12]. In invasive breast cancers, HIF-1α has been also associated with the expression of growth factors such as basic fibroblast growth factor (bFGF), platelet derived growth factor-B chain (PDGF-BB), and epidermal growth factor receptor (EGFR) [13]. HIF-1α may also be responsible

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for increased production of VEGF which enhance tumor vascularization in HER2 overexpressed cells and HER2 positive breast tumors [14, 15]. Interestingly, absence of high levels of HIF-1α protein expression has been detected by immunohistochemistry in the normal breast epithelium [7].

It has been thought that overexpression of HIF-1α could be the result of increased transcription of the gene or alteration in the degradation pathway [11, 16]. Interestingly, C1772T and G1790A polymorphisms which have been detected within the oxygen-dependent degradation (ODD)/pVHL binding domain in exon 12 of the HIF-1α gene [17] cause a significant higher transcriptional activity than the wild-type [3]. The polymorphic variants of C1772T and G1790A polymorphisms cause changes from proline to serine and alanine to threonine at codon 582 (P582S) and 588 (A588T), respectively. Presence of these variants in this critical regulatory domain may result in the overexpression of this protein, and subsequent changes in the expression of downstream target genes. In addition, another polymorphism, C111A, has been detected at codon 28 (S28Y) of exon 2 that leads an amino acid change from serine to tyrosine. Several studies have reported associations between HIF-1α gene polymorphisms and several types of cancer like head and neck [3], non-small cell lung [10], renal cell carcinoma [18], androgen-independent prostate [19], colorectal [20] and cervical and endometrial cancers [21]. Although HIF-1α plays pivotal roles in the development and progression, and tumor aggressiveness of several cancer types including breast cancer [11], to date there have been only a small number of published studies regarding the relationship between HIF-1α polymorphisms and breast cancer.

To the best of our knowledge, there was no epidemiological study that have been investigated on the existence of the C1772T, G1790A and C111A polymorphisms in HIF-1α gene in Malaysian breast cancer patients and normal subjects. According to the National Cancer Registry of Malaysia 2003, female breast cancer is the most common cancer among Malaysian women [22]. In the present study, we determined the genotype and allele frequencies of C1772T, G1790A and C111A polymorphisms in breast cancer cases and normal controls, and evaluated the association between these polymorphisms and breast cancer risk in a hospital-based Malaysian population. We also investigated the relationship between the polymorphic alleles of HIF-1α gene with established clinicopathological parameters such as ER status, nodal status, age at diagnosis and histological grading.

Materials and methods

Patients and tissues. Peripheral blood samples were collected from 410 women who were histologically confirmed as having breast cancer. Written informed consent was obtained from these patients who were admitted to University Malaya Medical Center, University of Malaya, Malaysia before proceeding further for collection of blood. The approval has been obtained from the Medical Ethics Committee of University Malaya Medical Centre. A total of 275 women who were healthy and had no history of breast disease or a family history of breast cancer were recruited as normal controls. The clinicopathologic characteristics of the patients were obtained from the pathology report of each patient. Histopathological evaluation of the tissues confirmed that 410 patients had invasive ductal carcinoma. Two hundred and eight invasive carcinomas were ER positive, 190 were ER negative, 187 were lymph node positive and 215 were lymph node negative. All the invasive ductal carcinomas were graded according to the modified criteria as described by Elston and Ellis, [23] and Bloom and Richardson, [24]. Well differentiated (Grade I) tumors were observed in 32 cases, moderately differentiated (Grade II) in 164 cases and poorly differentiated (Grade III) in 141 cases. Estrogen receptor status, lymph node status and histological grading were not available for 12, 8 and 73 patients, respectively. In Malaysia, the age pattern in 2003 showed that the age specific incidence rate peaks in 50-59 years age group [22]. Therefore, in the present study the patients were grouped based on age at diagnosis: age < 50 years and age ≥ 50 years. A total of 169 patients and 114 normal controls were less than 50 years old, and 240 patients and 161 normal controls were 50 years and above. Age at diagnosis was not available for one patient.

Genotyping at nucleotides C1772T, G1790A and C111A of HIF-1α gene. Genomic DNA was isolated from the peripheral blood samples according to the method provided by the manufacturer with some modification using PUREGENE Genomic DNA Purification kit (Gentra, USA) as described previously [25].

The polymorphisms at nucleotides C1772T, G1790A and C111A of HIF-1α gene were analyzed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method and the primer sequences as described by Ollerenshaw et al. [18] and Konac et al. [21], respectively. The primer sequences used to amplify the polymorphic sites of C1772T and G1790A (346 bp) were as follows: fwd: 5'-AAG GTG TGG CCA TTG TAA AAA CTC-3', rev: 5'-GCA CTA GTA GTT TCT TTATGTATG-3'. For the C111A (187 bp), the pair of primers were: fwd: 5'-GGA TAA GTT CTG AAC GTC GA -3', rev: 5'-ATC CAG AAG TTT CCT CAC AC -3'. Each PCR amplification was performed in a 50 ml reaction mixture containing 100 ng genomic DNA, 1X PCR buffer [50 mM KCl, 10 mM Tris-HCl (pH 8.3), 1.5 mM $MgCl_2$], 250 mM each of dGTP, dCTP, dTTP and dATP, 0.2 mM of each primers and 2.5 U of AmpliTaq DNA polymerase (Fermentas, Lithuania). The samples were amplified in a thermalcycler (MyCycler, BIO-RAD, USA). The PCR cycling parameters for C1772T and G1790A was 94°C for 4 min. followed by 35 cycles of 94°C for 30 sec., 57 °C for 1.5 min., 72 °C for 1.5 min. and final cycle at 72 °C for 7 min. The PCR cycling conditions for C111A was 94°C for 4 min. followed by 30 cycles of 94°C for 30 sec., 60 °C for 30 sec., 72 °C for 30 sec. and final cycle at 72 °C for 7 min. In each PCR run, DNA was substituted with sterile deionized water as a negative control. The PCR products were resolved

on 2% agarose gel and visualized by ethidium bromide staining to determine the presence of the amplicons.

For C1772T and G1790A, 7 µl of the same amplified PCR products were digested with *Hph*I (New England BioLabs, Beverly, MA, USA) at 37˚C for 4-5 hrs and *Aci*I (New England BioLabs, Beverly, MA, USA) at 37˚C for 4-5 hrs, respectively. The digested products were separated on 2.5% agarose gel. The restriction digest for C1772T reveals 228 and 118 bp fragments in the presence of C allele, and the product is uncut in the presence of T allele (346 bp). For G1790A, the G allele produces two bands, 201 and 145 bps whereas A allele abolishes an *Aci*I restriction site (346 bp). The polymorphic site for C111A was detected by digesting 7 µl of the PCR products with II (New England BioLabs, Beverly, MA, USA) at 37˚C for 4 hrs and resolved using 2.5% agarose gel. The 187 bp amplicons were not digested if A allele is present, but cleaved into 143 bp and 44 bp fragments when C allele is present.

Immunohistochemistry. The immunohistochemistry of estrogen receptor was performed using the DAKO EnVision™ System (Dako, Denmark) according to the manufacturer's guidelines. The immunostaining method has been described previously [25].

Statistical analysis. Analysis of data was performed using Epi Info (version 6.0, Atlanta, USA). The odds ratio (OR) and its 95% confidence interval (CI) were used to determine the correlation between the genotypes or alleles of HIF-1α polymorphisms and breast cancer risk. The significance of association between the observed and expected number of the genotypes for a population in the Hardy-Weinberg equilibrium was analyzed using the chi-square test. The test was also used to demonstrate the significant difference of genotype and allele frequencies between the breast cancer cases and normal controls, and also association between the genotype frequencies and clinico-pathological parameters. We used the Yates corrected chi-square test to calculate the P values. The 0.05 (5%) level of significance was used throughout the statistical test.

Results

The genotype and allele frequencies of HIF-1α polymorphisms in the breast cancer cases and normal controls in a hospital-based Malaysian population were shown in Table 1. The genotype frequencies of C1772T, G1790A and C111A polymorphisms in both the breast cancer cases (P=0.485, P=0.793, P=0.606) and controls (P=1.00, P=1.00, P value was not calculated) showed no significant deviation from the Hardy-Weinberg equilibrium, respectively.

The genotype frequencies of C1772T polymorphism were significantly different between the breast cancer cases and normal subjects (P=0.0093). We noted significant increase in the frequencies of CT (24.3%), TT (3.9%) and T allele genotype (CT + TT) (28.2%) in breast cancer cases as compared to the frequencies of CT (18.2%), TT (1.1%) and T allele genotype (19.3%) observed in normal individuals. Our data showed that women who were homozygous (OR=4.03; 95% CI, 1.09-17.60) or heterozygous (OR=1.51; 95% CI, 1.01-2.25) for T allele or carriers of T allele genotype (OR=1.65; 95% CI, 1.13-2.43) were significantly associated with increased breast cancer risk. The distribution of C and T allele frequencies was significantly different between breast cancer patients and the normal individuals (P=0.0024). Carriers of a T allele were more frequent among breast cancer patients (16%) than among the normal individuals (10.2%). Individuals who were carriers of T allele (OR=1.69; 95% CI, 1.20-2.40) showed an increased risk of developing breast cancer.

We found no significant difference in the distribution of G1790A genotypes and allele frequencies between the cancer patients and normal subjects (P=0.428 and P=0.235, respectively). We noted that the frequencies of GA, AA and A allele genotype (GA+AA) were 17.6%, 1.5% and 19.1% in breast cancer cases and 14.9%, 0.7% and 15.6% in normal subjects, respectively. Individuals with the homozygous AA (OR=2.10; 95% CI, 0.38-15.14) and heterozygous GA (OR=1.23; 95% CI, 0.79-1.91) genotypes were not significantly associated with breast cancer risk. Similarly, women who were carriers of A allele genotype (GA+AA) (OR=1.27; 95% CI, 0.83-1.95) and A allele (OR=1.28; 95% CI, 0.86-1.91) were also not associated with an increased risk of breast cancer.

As for C111A we were not able to observe AA genotype variant but noted very low frequency of CA genotype among the breast cancer patients and normal subjects (0.7% and 0.4%, respectively). As a result we were not able to determine the significant difference between the genotypes as well as to calculate the odds ratio for AA genotype. No significant risk of developing breast cancer was associated with individuals carrying CA genotype (OR=2.02; 95% CI, 0.19-50.63) or carriers of A allele genotype (OR=2.02; 95% CI, 0.19-50.63). Similarly, no statistically significant difference was found for allele frequencies of C and A between the cases and the controls (P=0.914). Women who were carriers of A allele were not significantly associated with increased risk of breast cancer (OR=2.02; 95% CI, 0.19-50.39).

Table 2 summarizes the relationship between the C1772T, G1790A or C111A genotypes and clinico-pathological parameters such as ER status, lymph node involvement, histological grade and age at diagnosis. Patients who were carriers of T allele genotype of C1772T polymorphism showed significant association with lymph node metastases than those with CC genotype (P=0.0478). We noted that the frequencies of the T allele genotype were higher in the lymph node positive (51.7%) than in the lymph node negative (42.2%) patients whereas CC genotype was represented more frequently in node negative (56.5%) compared with node positive (43.2%) patients. Significant difference was not observed in patients with ER status (P=0.315), histological grade (P=0.0958) and patients' age (P=0.308). With regard to G1790A and C111A genotypes, no significant relationship was seen with ER status (P=0.228 and P=0.279), nodal status (P=0.187 and P=0.903), tumor grade (P=0.678 and P=0.651) and age at diagnosis (P=0.275 and P=0.138), respectively.

Table 1 Distribution of HIF-1α allele and genotype frequencies in breast cancer cases and the control group

	Cases No. (%)	Controls No. (%)	OR (95% CI)	χ^2 P*-value
C1772T Genotype	(n=410)	(n=275)		
CC	294 (71.8)	222 (80.7)*	**1.00 (reference)**	**P=0.0093**+
CT	100 (24.3)	50 (18.2)	**1.51 (1.01-2.25)**	**P=0.0423**
TT	16 (3.9)	3 (1.1)	**4.03 (1.09-17.60)**	**P=0.0335**
T Carrier (CT + TT)	116 (28.2)	53 (19.3)	**1.65 (1.13-2.43)**	**P=0.0095**
Alleles	No. of alleles (n=820)	No. of alleles (n=550)		
C	688 (84.0)	494 (89.8)	**1.00 (reference)**	
T	132 (16.0)	56 (10.2)	**1.69 (1.20-2.40)**	**P=0.0024**
G1790A Genotype	(n=410)	(n=275)		
GG	332 (80.9)	232 (84.4)*	1.00 (reference)	P=0.428+
GA	72 (17.6)	41 (14.9)	1.23 (0.79-1.91)	P=0.392
AA	6 (1.5)	2 (0.7)	2.10 (0.38-15.14)	P=0.575
A Carrier (GA + AA)	78 (19.1)	43 (15.6)	1.27 (0.83-1.95)	P=0.299
Alleles	No. of alleles (n=820)	No. of alleles (n=550)		
G	736 (89.8)	505 (91.8)	1.00 (reference)	
A	84 (10.2)	45 (8.2)	1.28 (0.86-1.91)	P=0.235
C111A Genotype	(n=410)	(n=275)		
CC	407 (99.3)	274 (99.6)*	1.00 (reference)	Not calculated+
CA	3 (0.7)	1 (0.4)	2.02 (0.19-50.63)	P=0.914
AA	0 (0)	0 (0)	Not calculated	Not calculated
A Carrier (CA + AA)	3 (0.7)	1 (0.4)	2.02 (0.19-50.63)	P=0.914
Alleles	No. of alleles (n=820)	No. of alleles (n=550)		
C	817 (99.6)	549 (99.8)	1.00 (reference)	
A	3 (0.4)	1 (0.2)	2.02 (0.19-50.39)	P=0.914

Note: '+' represents chi-square analysis between breast cancer cases and normal controls for HIF-1α genotypes
'*' represents significance at P<0.05

Discussion

Our results indicated that the genotype and allele frequencies of C1772T polymorphism among the breast cancer cases were significantly different from the normal individual groups. This statistical association was further supported by our data which showed significant increase in the frequencies of CT, TT and T allele genotype (CT + TT) in breast cancer cases as compared to the frequencies of these genotypes observed in normal individuals. Similarly, there was higher representation of the T allele among the cases compared with the normal individuals. When we compared our data with other breast cancer studies the CT and TT genotypes and T allele were more frequent in the present study compared to the frequencies observed in Korean (8.9%; 0.5%; 4.9%) and Turkish (21%; 2%; 12%) women, respectively [26, 27]. Schneider et al. [28] reported that the frequency of the minor allele T among the Caucasians were 10% and among the African-American were 2%. In contrast to the present study, the distribution of genotype and allele frequencies between the controls and breast cancer cases were not significantly different among the Turkish [26] as well as among the Korean women [27]. Our study showed that women who were TT homozygote and CT heterozygote were associated with increased risk of breast cancer. Similarly, individuals who were carriers of T allele genotype or T allele also showed association with breast cancer risk. Among the Korean women, Lee et al. [27] reported a 5-fold increase in breast cancer risk to individuals having TT geno-

Table 2 Association between genotype frequencies of the HIF-1α polymorphisms and clinico-pathological parameters of the breast cancer patients

Clinico-pathological parameters	Total no. of cases (n=410)	C1772T		G1790A		C111A	
		CC (%)	CT+TT (%)	GG (%)	GA+AA (%)	CC (%)	CA+AA (%)
		(n=294)	(n=116)	(n=332)	(n=78)	(n=407)	(n=3)
Estrogen Receptor (ER) Status							
ER+	208	156 (53.1)	52 (44.9)	175 (52.7)	33 (42.3)	205 (50.4)	3 (100.0)
ER-	190	133 (45.2)	57 (49.1)	150 (45.2)	40 (51.3)	190 (46.7)	0 (0)
N/A+	12	5 (1.7)	7 (6.0)	7 (2.1)	5 (6.4)	12 (2.9)	0 (0)
		P=0.315		P=0.228		P=0.279	
Lymph Node (N) Status							
N+	187	127 (43.2)	60 (51.7)	145 (43.7)	42 (53.8)	185 (45.5)	2 (66.7)
N-	215	166 (56.5)	49 (42.2)	179 (53.9)	36 (46.2)	214 (52.6)	1 (33.3)
N/A+	8	1 (0.3)	7 (6.1)	8 (2.4)	0 (0)	8 (1.9)	0 (0)
		P=0.0478		P=0.187		P=0.903	
Histological Grade							
Grade I	32	24 (8.2)	8 (7.0)	24 (7.2)	8 (10.2)	32 (7.9)	0 (0)
Grade II	164	125 (42.5)	39 (33.6)	134 (40.4)	30 (38.5)	163 (40.1)	1 (33.3)
Grade III	141	92 (31.3)	49(42.2)	114 (34.3)	27 (34.6)	141 (34.6)	0 (0)
N/A+	73	53 (18.0)	20 (17.2)	60 (18.1)	13 (16.7)	71 (17.4)	2 (66.7)
		P=0.0958		P=0.678		P=0.651	
Age at Diagnosis							
< 50 years	169	116 (39.5)	53 (45.7)	132 (39.8)	37 (47.4)	166 (40.8)	3 (100.0)
≥ 50 years	240	177 (60.2)	63 (54.3)	199 (59.9)	41 (52.6)	240 (59.0)	0 (0)
N/A+	1	1 (0.3)	0 (0)	1 (0.3)	0 (0)	1 (0.2)	0 (0)
		P=0.308		P=0.275		P=0.138	

Note: N/A: not available; not included in the statistical analysis.
'+' represents values that are not included in the chi-square analysis.
'*' represents significance at P<0.05

type compared to CC genotype, although it was not supported statistically. Our data showed that women with TT genotype were associated with a 4-fold increase in breast cancer risk. However, Apaydin et al. [26] found that carriers of T allele (CT, TT and CT+TT genotypes) were not at risk of developing breast cancer. Furthermore, Schneider et al. [28] reported that presence of the C1772T polymorphic allele was not associated with the likelihood of developing breast cancer.

With regard to G1790A and C111A polymorphisms, we noted no significant differences between the breast cancer cases and the healthy individuals in terms of the distribution of genotypes and allele frequencies. Our data revealed higher frequencies of GA (17.6% and 14.9%) and AA (1.5% and 0.7%) genotypes, and A allele (10.2% and 8.2%) in the cases than in the controls, respectively. As for C111A polymorphism, we detected very low frequency of CA genotype in cancer patients (0.7%) and normal individuals (0.4%) but none was detected for AA variant. Interestingly, a recent study by Apaydin et al. [26] demonstrated absence of GA and AA variants in breast cancer patients and normal individuals except for GA genotype which was detected in 4% of the normal subjects. In the same population the authors also noted lack of CA and AA genotypes in the patients as well as the controls. Schneider et al. [28] observed 1790A allele in 1% of the Caucasian female population but none was detected in the African-American population. Consistent with other studies [26, 28], our data indicated that G1790A and C111A polymorphisms were not associated with increased risk of breast cancer. Our data suggests individuals who were carrying T allele of C1772T polymorphism may have increased susceptibility to breast cancer while polymorphisms of G1790A and C111A may not increase the risk of breast cancer development in Malaysian

female population. Presence of T allele may influence the biological behaviour of cells, thus increases the risk of developing cancer.

Based on clinico-pathological analysis, we noted that T allele genotype of C1772T polymorphism was significantly associated with lymph node metastases but not with estrogen receptor status and histological grade. Significant correlation was not observed between G1790A or C111A polymorphisms and clinico-pathological parameters in breast cancer patients. Stratification based on age at diagnosis revealed no evidence of association between C1772T, G1790A or C111A polymorphisms and women younger than 50 or 50 years and older. Although the age specific incidence rate is the highest in the 50-59 age group, no statistical association was observed between HIF-1α polymorphisms and age at diagnosis. This suggests that the role of HIF-1α polymorphisms in the development of breast cancer may be independent of patients' age. Tanimoto et al. [3] demonstrated tumors with C1772T variant showed enhanced transcriptional activity of HIF-1α under normotoxic conditions and increased tumor microvessel density. Furthermore, HIF-1α is an important inducing factor of VEGF, and was shown to enhance tumor vascularization by increasing the expression levels of VEGF [14, 15]. Recently, Kim and coinvestigators [29] using paraffin-embedded tissues demonstrated that overexpression of HIF-1α protein was significantly associated with the T1772 polymorphic allele. The authors also showed that increased levels of HIF-1α protein were associated with lymph node metastasis and high histological grade. This observation further supports our data which suggests that presence of T allele may promote tumor metastases. However, Apaydin et al. [26] found that HIF-1α polymorphisms were not associated with clinico-pathologic characteristics of breast cancer such as tumor grade, nodal status and age at diagnosis. In another study, Lee et al. [27] performed an analysis on the distribution of genetic polymorphism of C1772T and breast cancer risk by clinico-pathological parameters. The authors found that TT genotype was significantly associated with breast cancer risk in the group of patients without lymph node involvement. Our results were not comparable with the latter because of the different approach used in the data analysis. It has been well documented that tumors demonstrate lack of estrogen receptor, nodal metastases and poorly differentiated were associated with poor prognosis and worse clinical outcome. In the present study, an association with nodal metastases suggests that 1772T allele may have a role in tumor metastases and potential to be an indicator for poor prognosis but 1790A and 111A alleles may not be useful markers for tumor prognosis.

The discrepancy between the studies could be attributed to several factors such as study design, sample size, heterogenous ethnic background, and genetic factors within the ethnic groups that predispose them to breast cancer. In conclusion, our findings suggest that among the polymorphisms of HIF-1α gene, individuals carrying the polymorphic allele of C1772T may have a higher risk of developing breast cancer, and presence of 1772T allele may have potential to be a genetic marker for tumor prognosis. However, G1790A and C111A polymorphisms may not be related to breast cancer risk. Larger independent studies are warranted to demonstrate the significance and potential clinical implications of these polymorphisms in breast cancer.

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