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# The Association between the C1772T Genetic Polymorphism in Human *HIF-1 α* Gene and Breast Cancer Risk: A Meta-analysis

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## Abstract

**Purpose:** This meta-analysis aims to investigate the association between the C1772T genetic polymorphism in human *HIF-1α* gene and breast cancer risk.

**Methods:** PubMed and Embase databases were searched till October 2013 to identify eligible studies. A total of 2143 cases and 2046 controls from 6 studies were included in this paper. Allelic and genotypic comparisons between cases and controls were evaluated. Subgroup analyses by ethnicity were also performed.

**Results:** The recessive model, dominant model, comparison suggested that the genotype C1772T polymorphism was not significant without the increased breast risk: OR=1.38 [95% CI (0.35, 5.46)], P=0.65 and OR=1.14 [95% CI (0.83, 1.55)], P=0.43, respectively. The results for the co-dominant model comparison were not different with the results as follows: OR=1.10 [95% CI (0.83, 1.46)], P=0.50 and OR=1.41 [95% CI (0.34, 5.75)], P=0.64, respectively. The data of the allele results with OR=1.09 [95% CI (0.80, 1.48)], P=0.59, were not significant. Subgroup analyses by ethnicity were performed in the co-dominant model (TT versus CC)recessive model, and the allele model with the increased breast cancer risk in the Asia: OR=4.42 [95% CI (1.60, 12.21)], P=0.004, and OR=4.16 [95% CI (1.51, 11.48)], P=0.006, and OR=1.28 [95% CI (1.05, 1.55)], P=0.01, respectively.

**Conclusions:** This meta-analysis suggests that the C1772T polymorphism is significantly associated with breast cancer risk in Asia. However, we find that the C1772T polymorphism is not associated with breast cancer risk on the whole.

**Keywords:** HIF-1α; Polymorphism; Breast cancer; Meta-analysis

## Introduction

Breast cancer is the most common malignant tumor and the main cause of death by cancer among women in both developed and developing countries [1,2]. The exact mechanism of carcinogenesis is not yet fully elucidated. As is shown now, breast cancer is a heterogeneous disease with probably multiple genetic abnormalities [3]. In the past few years, the relationship between genetic polymorphisms such as variants of pro-inflammatory, anti-inflammatory cytokines, and breast cancer risk has been extensively investigated [4].

As the incidence of cancer increased, a local hypoxic microenvironment is initiated as a result of perfusion defects. Conversely, the hypoxic microenvironment can lead to the development and progression of cancer by causing multiple cellar response, such as cell proliferation and local angiogenesis [5]. Hypoxia-inducible factor-1 (HIF-1), over-expressed in many solid cancer including breast cancer, is a key transcription, playing an essential role in the oxygen homeostasis. HIF-1 consists of an oxygen-regulated α subunit and a constitutively expressed β subunit, involving in angiogenesis [6], energy metabolism [7], extra-cellular matrix remodeling [8], and cell response (e.g. cell proliferation, migration and invasion) etc., [9] by activating associated gene expression. Recent studies have shown that HIF-1α is over expressed as an independent prognostic factor, which is associated with an aggressive phenotype and increased mortality in many cancer types, including breast cancer [10].

The human *HIF-1α* gene, which is located at chromosome 14q21–24, is composed of 15 exons. It encodes a 3919 bp cDNA and synthesizes an 826 amino acid protein. The C1772T (rs11549465) polymorphism, which is the most common polymorphisms and mutations within HIF-1α gene, has been identified [11]. It corresponds to a proline to serine amino acid substitution at codon 582. Many studies have investigated the influence of the C1772T polymorphism on breast cancer risk but the results have been remaining conflicting [12,13]. Therefore, the association between the C1772T polymorphisms and breast cancer requires further study. In this paper, a meta-analysis combining all available data is conducted to estimate the potential associations of C1772T polymorphisms with breast cancer risk.

## Methods

### Search strategy for identification of studies

All studies published before October 1st, 2013 that investigated the association of the C1772T polymorphisms with breast cancer risk were considered in this meta-analysis. A systematic search of the literature

was carried out by using PubMed and Embase. The MeSH terms were used as follows: "Breast Neoplasm" AND "Hypoxia-Inducible Factor 1 or hypoxia-associated factor, human or Hypoxia-Inducible Factor 1, alpha Subunit" AND "Polymorphism, Genetic or Polymorphism, Single Nucleotide". Meanwhile, the keywords terms were used to supplement: "lacteal gland or mammary gland or breast" AND "HIF-1 or hypoxia-inducible factor-1" concatenated with "polymorphism or variant or SNP or mutation" AND "cancer OR tumor OR carcinoma OR malignancy". No restriction was applied. Only the studies with complete data on comparison of frequency of the C1772T polymorphisms between controls and patients with breast cancer were selected. Review articles, abstracts, editorials, animal studies, case reports, reports with incomplete data, and studies based on pedigree data were excluded.

## Data extraction

Two investigators extracted information from all eligible articles independently according to the inclusion criteria. When overlapping articles were found, we only selected the article that included the most extensive information. Disagreements were resolved by discussion and consensus between the investigators. A third investigator was consulted to reach a consensus if any dispute occurred. The data extracted were as follows: the first author's name, publication year, country, ethnicity, source of control, the number of cases and controls, whether genotype distribution of the control population was in Hardy–Weinberg equilibrium (HWE) (Table 1).

| Author | Year | Country | Ethnicity | Case/Control | Source of control | In HWE or not |
|---|---|---|---|---|---|---|
| R. Naidu | 2009 | Malaya | Malaysia | 410/275 | Hospital-based | In |
| Evans CE | 2012 | Greece | Caucasian | 113/124 | Hospital-based | In |
| Ana Luísa | 2013 | Portugal | Portuguese | 96/74 | Hospital-based | In |
| Ji-Young Lee | 2008 | Korea | Korean | 1599/1536 | Hospital-based | In |
| Isil Apaydin | 2008 | Turkey | Caucasian | 102/102 | Hospital-based | In |
| Vainrib M | 2008 | Korea | Korean | 90/102 | Hospital-based | In |

**Table 1:** Characteristics of studies included in this meta-analysis.

## Statistical analysis

Review Manager 5.1 software (The Cochrane Collaboration, Oxford, UK) was used for meta-analysis. The summary ORs and their corresponding 95% CI were calculated to assess the strength of the association between the C1772T polymorphism and breast cancer risk. The Cochrane Q-test was used to assess the heterogeneity among the included studies. The I2 statistics were used to measure heterogeneity. In this study, the Fix-effects model (the Mantel–Haenszel method) was selected. The genotype distribution of the control population in all the included studies was in Hardy–Weinberg equilibrium (HWE). The publication bias was estimated by visually assessing the asymmetry of funnel plots. A symmetric plot indicated no publication bias. By contrary, an asymmetric plot indicated a possible publication bias. Furthermore, Egger's test was performed to provide quantitative evidence for the checking of publication bias if an asymmetric plot occurred.

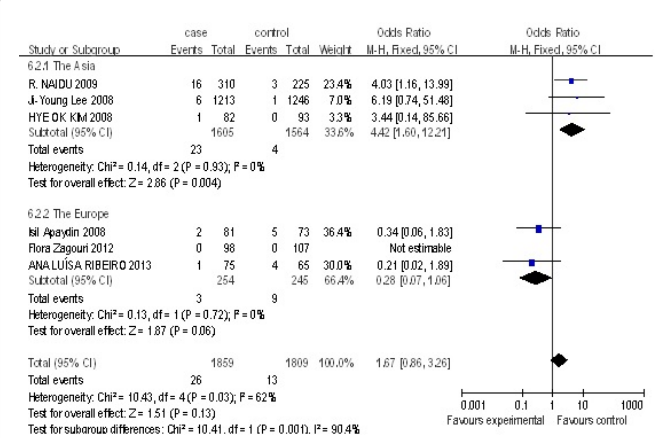


**Figure 1:** Forest plots the C1772T genetic polymorphism and breast cancer risk in codominant model (TT versus CC) of the ethnicity subgroup.

# Results

## Summary statistics

The meta-analysis for the C1772T polymorphism of HIF-1α included 2143 cases and 2046 controls. In both case and control groups, the prevalence of the CC genotype was the highest, allele C was the most frequent, and the prevalence of the TT genotype was the lowest.

## The association between the HIF-1α C1772T polymorphism and breast cancer risk

The meta-analysis was performed on all 6 studies. The results for the recessive model, dominant model, comparison suggested that the genotype the C1772T polymorphism were not significant without the increased breast risk: OR=1.38 [95% CI (0.35, 5.46)], P=0.65, Pheterogeneity=0.04, I2=60%, and OR=1.14 [95% CI (0.83, 1.55)], P=0.43, Pheterogeneity=0.10, I2=46%, respectively.

The results for the co-dominant model (CT versus CC, TT versus CC) comparison were not different with the results as follows: OR=1.10 [95% CI (0.83, 1.46)], P=0.50, Pheterogeneity=0.16, I2=37%, and OR=1.41 [95% CI (0.34, 5.75)], P=0.64, Pheterogeneity=0.03, I2=62%, respectively. The data of the allele results with OR=1.09 [95% CI (0.80, 1.48)], P=0.59, Pheterogeneity=0.04, I2=56% were not significant, too. Subgroup analyses were performed to estimate the effect of the ethnicity and evaluate the high heterogeneity [co-dominant model (TT versus CC), recessive model (TT versus CT +CC), and the allele model (T versus C)]. We find the significant association between the 1772C/T polymorphism and breast cancer risk in the Asia with the co-dominant model(TT versus CC), OR=4.42 [95% CI (1.60, 12.21)], P=0.004, Pheterogeneity=0.72, I2=0% (Figure 1) and recessive model (TT versus CT+CC), OR=4.16 [95% CI (1.51, 11.48)], P=0.006, Pheterogeneity=0.91, I2=0% (Figure 2) and the allele

model (T versus C), OR=1.28 [95% CI (1.05, 1.55)], P=0.01, Pheterogeneity=0.11, I2=55%, respectively.

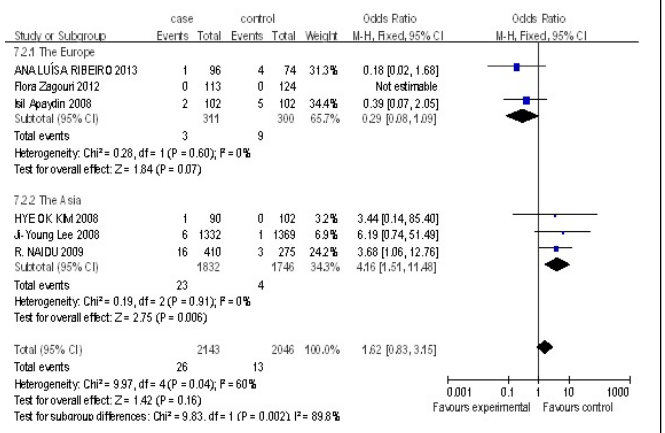


**Figure 2:** Forest plots the C1772T genetic polymorphism and breast cancer risk in recessive model (TT versus CT+CC) of the ethnicity subgroup.

Publication bias was evaluated by funnel plot inspection. The shape of the funnel plot seemed symmetrical, indicating the absence of publication bias (Figure 3).

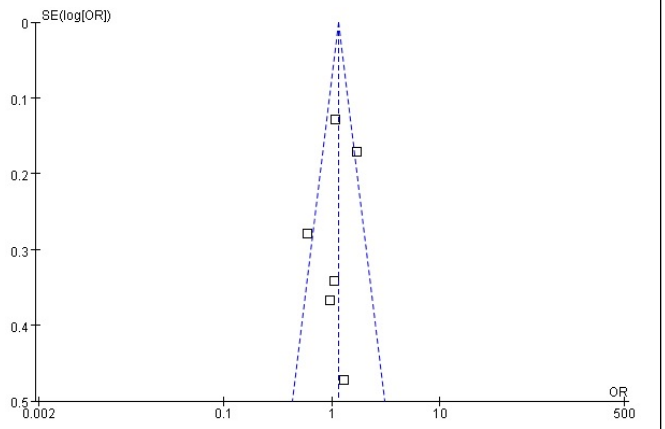


**Figure 3:** Begg's funnel plot for publication bias test: Begg's funnel plot with pseudo 95% confidence limits.

## Discussion

HIF-1 plays an important part in cancer progression and metastasis through altering tumor metabolism, which can influence cell adhesion, cell survival, regulation of angiogenesis and glucose transportation [14]. Recent studies have shown that a subunit of *HIF-1α* gene is over-expressed in breast cancer [15]. The C1772T polymorphisms are the most widely studied, which induce proline-to-serine amino acid substitutions and associated with increased HIF-1α expression in breast cancer [16]. The C>T change at 1772 causes the increase of Pro/Ser variation at codon 582 [17]. The C1772T is detected within the oxygen-dependent degradation (ODD)/pVHL binding domain in exon 12 of the *HIF-1α* gene [13]. The C1772T, especially genotypes with T allele (TT or CT) [18] is showed than it can strengthen a significant transcriptional activity of the *HIF-1α* [13]. There are reasons for the effect of The C1772T on HIF-1α. First, the C1772T may cause structural changes to enhance the transcriptional activity [13]. Second, the stability as well as expression of HIF-1α protein is increased and the expression of downstream target genes are influenced [19]. Third, the transcriptional co-factors such as CBP/p300 and SRC-1 that connect with HIF-1α by the variant forms *via* conformational changes are recruited actively [20]. In addition, Vainrib et al. reported that the C1772T mutation caused higher basal levels of HIF-1α mRNA [21]. It indicated that the polymorphisms might be implicated in the process of breast carcinogenesis by regulating the expression of HIF1α. And HIF-1a 1772 C/T genetic polymorphism has been considered to influence risk for many types of cancer.

Despite numerous efforts have been made to study the association between the HIF-1α polymorphisms and breast cancer risk, the results remain controversial [22,23]. Therefore, we conducted a comprehensive meta-analysis to explore the role of the C1772T polymorphisms in breast cancer risk. We investigated that the significant association between the 1772C/T polymorphism and breast cancer risk only in the Asia with the co-dominant model (TT versus CC), recessive model (TT versus CT+CC), and the allele model (T versus C). Moreover, it is showed that the C1772T polymorphism might cause breast cancer in Asia. In a comparison model through data analysis from 6 studies (2143 cases and 2046 controls studies), we showed that the C1772T polymorphism was not associated with increased breast cancer risk. Zhao et al. [24] performed a meta-analysis and explored the association between the C1772T polymorphism and cancer risk including breast cancer. The showed that the C1772T polymorphism was significantly associated with higher cancer risk in breast cancer, which was not consistent with our finding. Combining the results in this study, the C1772T polymorphisms may be associated with increased breast cancer risk in the Asia, but not in the Europe. Therefore, we suggested that HIF-1α polymorphism as a potential marker in breast cancer risk in the Asia. Though we did not explored the association between the HIF-1α polymorphism and the prognosis, the C1772T polymorphisms might perform in breast cancer prognosis. Since there is obvious heterogeneity in some comparison models, subgroup analysis by ethnicity were performed the present meta-analysis. In the subgroup study, it was reported that the ethnicity affects cancer susceptibility significantly. The results can be explained through the difference in genetic background, environmental exposure, and risk factors relating to lifestyle between the Asia and the Europe. However, there are some strong advantages in our meta-analysis, the sample size and number of studies included in the study are major limitations. Therefore, more updated data regarding the C1772T polymorphisms and breast cancer risk should be estimated the potential association in the future. First, considering the more studies included and larger sample size combined, pooled ORs from our study were better. The association between The HIF-1α polymorphisms and breast cancer risk were shed light on. Second, all the studies were in HWE. Third, the subgroup analysis including ethnicity was performed to explain the high heterogeneity. And No publication bias was also found in the collected data.

In summary, we showed no association between HIF-1α C1772T polymorphisms and breast cancer risk on the whole. However, there are significant associations between the HIF-1α polymorphisms and breast cancer risk in the Asia. Therefore, more studies should be considered in the future to obtain a more comprehensive

understanding of the association between HIF-1α polymorphisms and breast cancer risk.

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