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Tumor necrosis factor-alpha and tumor necrosis factor beta polymorphisms and risk of breast cancer: Review

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ABSTRACT

We conducted a review to assess the association between tumor necrosis factor-alpha TNF α gene TNFα −308 (G/A), TNFα −238(G/A), and tumor necrosis factor-beta TNFβ +252 (G/A), polymorphisms and breast cancer (BC) susceptibility.

Thirty one eligible case–control studies with a total of 11,723 BCE patients and 11,024 controls for TNFα (−308 G/A; −238G/A) and 4268 BCE patients and 4071 controls for TNFβ (+252G/A) were identified.

We found a significant association between TNFα (−308 G/A; −238G/A) and TNFβ (+252G/A) polymorphism and BC susceptibility in 15 studies, However, we found no significant association between TNFα and TNFβ polymorphism and breast cancer susceptibility in 16 studies.

In conclusion, further large, well-designed, and epidemiological studies are necessary to clarify the role of these polymorphisms in BC.

List of abbreviations

TNF α	tumor necrosis factor-alpha
TNFβ	tumor necrosis factor-beta
BC	Breast Cancer
OR	Odds Ratio

1. Introduction

Breast cancer (BC) is a disease characterized by the presence of uncontrolled cell growth in the ducts (ductal carcinoma) or lobules (lobular carcinoma) of the mammary gland. These tumors can invade the surrounding tissues of the breast in later stages. Most breast tumors are invasive or infiltrating, and they are classified by the World Health Organization with several defined stages.

BC is one of the most common diseases in the world as well as a major health problem owing to its social implications, high health costs for states, and increasing incidence rates of the diagnosis each year (Bandi et al., 2010).

An estimated 1.67 million cancer cases diagnosed in 2012 (25% of all cancers), among all types of cancer, breast cancer has the fifth highest mortality rate. It is the most frequent cancer-related cause death among women in developing countries, and the second most frequent among women in developed countries after lung cancer (Globocan(International Agency for Research on Cancer), 2012) and one of the important contributors to the global health burden (Isabelle et al., 2012).

BC is considered a multifactorial disease, previous research has implicated a variety of risk factors for BC, including age, early menarche, menopause, oral contraceptive use, cigarette smoking, alcohol consumption, and family history of BC, breast fibrosis, ethnicity, nutrition, and genetics, it might result from a combination of abnormal protein levels and their interaction with environmental factors. Therefore more recognition of risk factors is important in its prevention (Abdulrahman and Rahman, 2012) (Washbrook, 2006).

The mechanisms underlying breast cancer are still far from fully understood, several genetic polymorphisms have been reported to associate with disease. The genetic factors play important role in the epidemiology and pathogenesis of cancer and could provide targets for the future development of new therapies.

Germline mutations in high-penetrance susceptibility cancer genes, such as Breast Cancer 1 (BRCA1) and Breast Cancer 2 (BRCA2), account for only 5%–10% of all breast cancer cases, whereas the cause of most of the cases are low-penetrance cancer genes, such as cytokines

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(Sunpaweravong and Sunpaweravong, 2005). Although low penetrance cancer genes have low risk for breast cancer, their variants are relatively common in the population (Weber and Nathanson, 2000). To date many reports have been published on common low-penetrant genes associated with an increased breast cancer risk (Dunning et al., 1999). An important one is tumor necrosis factor (TNF).

TNF is a key angiogenic molecule that may promote angiogenesis directly by stimulating endothelial cell proliferation and indirectly by modulating expression of other proangiogenic factors (Leek et al., 1998). Moreover, TNF is known to induce expression of adhesion molecules thought to be involved in the increased motility and invasive/metastatic behavior of tumor cells (Ioculano et al., 1995).

The polymorphisms of cytokine genes tumor necrosis factor alpha (TNF-α), and tumor necrosis beta (TNF-β) are associated with many diseases, including cancer (Hollegaard and Bidwell, 2006).

1.1. Polymorphism of tumor necrosis factor alpha and breast cancer

TNFα is a multifunctional cytokine that has both protumorigenic and antitumorigenic characteristics (Balkwill, 2002). High-dose local administration of TNF-α destroys tumor blood vessels and has powerful anticancer activity, but, when chronically produced, the cytokine may act as an endogenous tumor promoter, contributing to tissue remodeling and stromal development necessary for tumor growth and spread (Balkwill, 2002).

The TNF-α gene is located on the short arm of chromosome 6 (6p21.3) (Pennica et al., 1984).

Several polymorphisms in the promoter region of this gene have been associated with different TNF-α expression levels (Kirkpatrick et al., 2004). The most common of this variant is G > A polymorphism located in −308 bp upstream from the start site of TNF-α gene (Wilson et al., 1992)

The TNF-α -308G > A polymorphism affects TNF-α expression the-308G allele produces less TNFα and 308A allele produces high TNF-α and this polymorphism is associated with high risk of breast cancer (Kroeger et al., 1997) (Wilson et al., 1997).

As to TNF α-238 polymorphism, it was reported to play an apparently protective role in cancers (Jang et al., 2001).

1.2. Polymorphism of tumor necrosis factor beta and breast cancer

The TNF β gene is located with TNFα on chromosome 6 in major histocompatibility complex and has similar biological activities (Smith et al., 1994).

The TNFβ -252A > G polymorphism, which is in the first intron of this gene, affects the TNFβ plasma level and in vitro TNFβ expression (Messer et al., 1991) (Ozaki et al., 2002).

This polymorphism is located in a phorbol ester-response element and shows a high affinity for activator protein-1, jun, and C-fos heterodimer transcription factor family.

In fact, numerous studies have investigated genetic polymorphisms and breast cancer susceptibility or progression. (Park et al., 2002) (Lee et al., 2005).

However, the association between breast cancer risk and polymorphisms found in TNF gene is still controversial.

Many studies have found that pro-inflammatory genotypes of TNFα and TNF β were associated with breast cancer risk (Gaudet et al., 2007). However, other studies have suggested that polymorphisms of TNFα or TNF β may not be significantly associated with breast cancer risk.

We performed a mini review of some eligible studies to better address the association between TNFα and TNFβ polymorphism with breast cancer risk.

2. Methods

The present review was carried out according to PRISMA guidelines (Moher et al., 2009).

2.1. Search and study selection

An extensive search was conducted in PubMed/Medline and web of science databases for articles that have been published until December 20, 2014, by using keywords related to BC (Breast cancer; TNF alpha; TNF beta; polymorphism). Based on the first screening of the titles and abstracts, the studies were selected. A full screen was conducted to exclude studies did not meet eligibility criteria.

2.2. Eligibility criteria

This current review includes all studies that met the following inclusion criteria:

- Published in peer-reviewed journal.
- Written in the English language.
- TNFα polymorphism and breast cancer susceptibility
- TNFβ and breast cancer susceptibility
- Results of TNFα and TNFβ polymorphism assessed separately or combined reported for each group (P value, OR, significant involvement).

3. Results

A total of 65 records were identified, from which 15 duplicates records were removed. Titles and abstracts of 50 records were screened and 20 records were excluded because they did not meet the defined eligibility criteria. The full texts of the remaining 30 reports were examined. After screening, 30 records were included in qualitative synthesis (Fig. 1). Totally 11,723 BCE patients and 11,024 controls were identified for TNFα (−308 G/A; −238G/A). In addition the associations of TNFβ (−252G/A) with BC susceptibility were evaluated using a total of 4268 BCE patients and 4071 controls. With totally 31 studies found a significant association between TNFα (−308 G/A; −238G/A) and TNFβ (−252G/A) polymorphism and BC susceptibility in 15 studies, However, we found no significant association between TNFα and TNFβ polymorphism and breast cancer susceptibility in 16 studies. The detailed characteristics of the studies were shown in the Table 1.

4. Discussion

Breast cancer (BC) is the second most frequent cancer in the world, which is the largest cause of deaths in the women. Though many studies show that BC onset and progression are multi-step processes resulting from a series of epigenetic, genetic, endocrine and external environmental factors, chronic inflammation was considered to play an important role in BC development.it may promote tumor progression through stimulation of the vascular endothelium via recruitment of leukocytes to the tumor, triggering angiogenic, mitogenic, and chemotactic factors and proteolytic enzymes that recruit other inflammatory cells to stimulate angiogenesis, which in turn sustains tumor growth and facilitates metastasis (Guadagni et al., 2007).

TNF-α has been identified as a pro-inflammatory molecule central to the regulation of inflammatory response. The function of TNF-α is complex; it interacts with 2 receptors, TNFR1 and TNFR2, which participate in signal transduction pathways and the signaling cascade of cellular responses such as apoptosis, proliferation, differentiation, migration, and angiogenesis (Cereda et al., 2012). Changes in single nucleotides in coding regions of the TNF-α promoter have been suggested to modify the binding site of specific transcription factors, and therefore affect transcriptional regulation and modulate their secretory responses.

LTA is a crucial proinflammatory cytokine, which has multiple