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Insulin-like Growth Factor 1 gene polymorphism and breast cancer risk

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ABSTRACT

Insulin-like Growth Factor-1 (IGF-1) gene polymorphism has been associated with an increased risk for breast cancer. IGF-1 is a key regulator of proliferation, cell differentiation and apoptosis. It has important mitogenic and anti-apoptotic activities in normal cells and in breast cancer cells, acting synergistically with estrogen to increase neoplastic cell proliferation. This review aims to present the recent finds of IGF-1 gene polymorphism and its relationship with the risk of breast cancer through following the polymorphic dinucleotide repeat cytosine-adenine (CA) and single nucleotide polymorphisms (SNPs) by searching in the PubMed database publications focused studies published from 2010 to 2015 related to IGF-1 gene polymorphism and breast cancer risk. A growing number of studies support an association between IGF-1 gene polymorphism and breast cancer risk with conflicting results, nevertheless elucidation of the patterns of IGF-1 gene expression may permit characterization of women at high-risk for breast cancer, as well as the development of strategies for early diagnosis and efficient treatment against the disease.

Key words: Breast cancer, risk factors, IGF-1, IGF-1 gene polymorphism.

INTRODUCTION

Breast cancer is the most common malignancy in women worldwide. It is the second most frequent neoplasm, excluding non-melanoma skin cancer. Incidence rates are higher in more developed regions, in comparison to developing regions of the world. Breast cancer rates vary from 27 cases per 100,000 women in eastern Africa to 96 cases per 100,000 women in western Europe (Ferlay et al. 2015).

Breast cancer etiology is unknown. However, it is a multifactorial disease and genetic factor is the main risk factor for the disease. It is well-known that breast cancer (BRCA) 1 and 2 gene mutations may increase the risk of developing hereditary breast and ovarian cancer over time (Mersch et al. 2015). Nevertheless, the participation of breast cancer genes has not been fully elucidated. Some authors

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have shown a significant association between IGF-1 gene polymorphism and breast cancer, however there is a need for further elucidation of the association between IGF-1polymorphism and increased risk of breast cancer (Sarkissyan et al. 2011, Sarfstein et al. 2012, Christopoulos et al. 2015).

IGF-1 is produced mainly by the liver and is directly stimulated by growth factor (GH) (Philippou et al. 2014). Insulin-like growth factor 1 and Insulin-like growth factor 2 (IGF-2) are part of a large family of peptide hormones. IGF-1 is a single-chain polypeptide, located on chromosome 12q22-q24 and formed by 70 aminoacids with a length of 100 kilobase (kb) and it contains 6 exons (Yu et al. 2001, Pavelić et al. 2007, Lelbach et al. 2005, Renehan et al. 2004). IGF-1 gene expression is controlled by both transcriptional and post-translational modifications. Therefore, diverse IGF-1 peptides may result from the use of different promoters, alternative splicing, proteolytic processing and glycosylation events (Denley et al. 2005).

IGF-1 is found in the majority of human tissues, such as in normal and malignant mammary glands, being mainly expressed by stromal and only rarely by epithelial cells (Macias and Hinck 2012). In combination with GH, insulin and sex hormones, IGF-1 is a crucial regulator of cell growth, differentiation and apoptosis. It has significant mitogenic and anti-apoptotic activities in breast cancer cells and acts synergistically with estrogen to promote tumor growth (Cleveland et al. 2006, Philippouet al. 2014, Gunter et al. 2009). These activities are mainly mediated by the transmembrane tyrosine-kinase of IGF-1 receptor (IGF-1R), that in contrast to IGF-1, it is expressed mainly in the mammary epithelium (Philippou et al. 2007), however IGF-1 is segregated by breast tissue for its differentiation from mammary connective tissue and adipocytes (Gonzalez-Zuloeta et al. 2007).

Circulating IGF-1 levels vary according to the age of the person, since initially, IGF-1 levels increase slowly from birth to puberty and later these levels decline with age in a stable manner, due to low GH levels (Philippou et al. 2007, Yu and Rohan 2000, Gennigens et al. 2006).

The half-life and bioavailability of circulating IGF-1 is regulated by a family of six IGF binding proteins (IGFBP1-6) (LeRoith and Roberts 2003) that control the distribution, function and activity of insulin-like growth factors in various cells, tissues and body fluids (Subramani et al. 2007). Each IGFBP may bind to IGF-1 with a high affinity and is regulated by various specific IGFBP proteases. Circulating IGF-1 binds mainly to IGFBP3 and only 1% remains unbound, generating a complex with an acid labile subunit (Pollak 2008).

Although IGF-1 levels may be affected by environmental factors and lifestyle, there is evidence that a significant level of IGF-1 expression may be influenced by genetic polymorphisms (Guntur and Rosen 2013).

Genetic variations are mainlycomposed of single nucleotide polymorphisms (SNPs) and these variations lead to genetic differences in susceptibility to breast cancer (Kang et al. 2014). Insulin-like growth factors types 1 and 2 are peptide growth hormones that promote epithelial cell proliferation in the normal and neoplastic breast (Sachdev and Yee 2001).

It is known that IGF-1 is associated with an increased risk of developing a number of cancers (Tsuchiya et al. 2013, Cao et al. 2014, Ong et al. 2014) including breast cancer (Wang et al. 2014, Gu et al. 2010). Thus, due to an increased risk of breast cancer caused by IGF-1 polymorphism and elevated IGF-1 levels and also the scarcity of studies on the subject, the aim of this review is to conduct a bibliographic research on IGF-1 gene polymorphism and its relationship with breast cancer risk.

MATERIALS AND METHODS

Literature searches were undertaken on PubMed database, by using a specific query. The base search strategy included the following search terms: Breast Neoplasms and Polymorphism Genetic, Breast Neoplasms and Insulin-Like Growth Factor 1, Polymorphism Genetic and Insulin-Like Growth Factor 1, Polymorphism Genetic and Breast Neoplasms and Insulin-like Growth Factor 1. The paper selection process included a two-step approach in which the screening of title and abstract was followed by the application of inclusion criteria to the full paper of the selected studies. Studies published from 2010 to 2015 related to the Insulin-Like Growth Factor 1 family and studies that explored the relationship between IGF-1 gene polymorphism and the risk for breast cancer, such as the study of polymorphic cytosine-adenine (CA) dinucleotide repeat sequences and SNP polymorphism were included. Case reports, animal studies, literature review, Meta analisys, letters to the editor and articles not in english were excluded.

RESULTS

As a result of the search, 3,393 papers were identified for initial screening. Of these, 876 satisfied the inclusion criteria. 867 studies were later excluded because eight of them were duplicate articles, 624 of them not envolved polymorphic cytosine-adenine (CA) dinucleotide repeat sequences and SNP polymorphism, 96 were literature review and 139 Meta analisys. Thus, only 9 studies were used in the review and Table I summarizes the studies published (Figure 1).

DISCUSSION

IGF-1 GENE POLYMORPHISM AND RISK OF BREAST CANCER

Population-based studies have shown that circulating IGF-1 levels, IGFBP-3 concentrations and genetic IGF-1 variations have been associated with cancer. Some Genome-Wide Association Studies (GWAS) identified various breast cancer susceptibility loci associated with risk of breast cancer Chang et al. 2012, Stacey et al. 2007, 2008, Easton et al. 2007) These susceptibility variants of low penetrance are commonly present in the population in general and when these variants are expressed individually, only a low risk for breast cancer exists. However, when these variants are combined in a polygenic model, the risk of developing cancer increases considerably (Dai et al. 2012, Harlid et al. 2012) In the last few years, there has been increasing interest in the study of genomic analysis of the IGF-1 gene in an attempt to identify specific alterations involved in tumor formation and progression, in particular in breast carcinoma. Two of the most widely studied genetic alterations of IGF-1 gene is a polymorphic cytosine-adenine (CA) dinucleotide repeat sequence and SNP polymorphism (Gu et al. 2010, Javadi et al. 2012, Muendlein et al. 2013, Qian et al. 2011)

Polymorphic CA dinucleotide repeat sequences may vary from 10 to 24 repeats in length, and CA 19 is the most common allele. This repeating sequence is located 1 kb upstream of the transcription initiation site and is thus considered a promoter polymorphism that is probably related to regulation of IGF-1 protein levels (Sarkissyan et al. 2011) Al-Ajmi et al. (2012) analyzing IGF-1 gene polymorphism (CA 19) by genomic DNA extracted from peripheral blood of 147 patients with breast cancer, found difference in cases and controls was significant among postmenopausal women ($p = 0.026$) and no significant association between CA 19 and risk of breast cancer among Arab Omani women in the premenopausal period ($p= 0.394$) with 95% confidence intervals. However, in another study of 268 African-American and Hispanic/Latin-American women with breast cancer, a significant correlation of the non-19 /non-19 allele genotype with breast cancer by univariate analysis (Odds Ra-

TABLE I
Description of the selected studies.

Author	Type of Study	Characteristic Population	Sample Size	Conclusion
Gu et al. (2010)	Case control	Caucasian Women	2080 breast cancer and 3453 controls	No significant association was observed between 302 SNPs of the IGF-1 gene and breast cancer.
Javadi et al. (2012)	Case control	Iranian Women	215 breast cancer and 224 controls	A strong association between the length of the allele polymorphism of the IGF-1 gene CA and the risk of breast cancer.
Muendlein et al. (2013)	Prospective cohort	Austrian Women	161 women HER2-positive breast cancer	A significant association between the polymorphism of the IGF-1 gene (rs 2946834) and a worse prognosis of patients with HER2-positive breast cancer.
Qian et al. (2011)	Case control	Chinese Women	403 breast cancer and 403 controls	A significant association between the polymorphism of the IGF-1 gene (rs7965399) and breast cancer in a recessive model, with greater association in premenopausal women with negative estrogen receptor tumors.
Canzian et al. (2010)	Case control	Caucasian Women	6292 breast cancer and 8135 controls	No association between the SNPs of the IGF-1 gene and the risk of breast cancer.
Henningson et al. (2011)	Cross-sectional	Swedish Women	325 women from breast cancer high-risk families	No SNP and diplotypes were associated with IGF-1, however rare diplotypes were correlated with the early development of breast cancer.
Sarkissyan et al. (2011)	Case control	African-American and Hispanic Women	268 breast cancer and 386 no breast cancer	A significant association between the polymorphism of the IGF-1 gene and the risk of breast cancer, especially for the polymorphism of alleles non 19/non19.
Al-Ajmi et al. (2012)	Case control	Omani women	147 cases and 134 control	No association between the polymorphism of the IGF-1 gene CA (19) and breast cancer in women of Oman.
Yaren et al. (2012)	Cross-sectional	Non-metastatic breast cancer patients, median age at disease onset was 49 years	76 patients	Polymorphism of the IGF-I gene can affect the prognosis of breast cancer, for patients with non-metastatic breast cancer patients with homozygous alleles non-19/non 19 had not a better prognosis.

SNPs: Single nucleotide polymorphisms; **IGF-1**: Insulin-like Growth Factor 1; **CA**: Cytosine-adenine; **HER2**: Human epidermal growth factor.

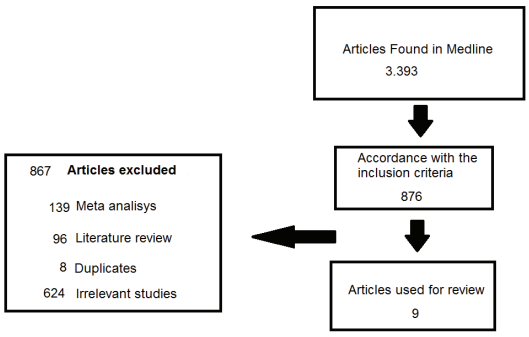

Figure 1 - Algorithm the database used.

tio (OR) = 1.75; 95% CI = 1.07-2.88; p=0.027). (Sarkissyan et al. 2011)

There is growing evidence that CA 19 allele is associated with an increased incidence of breast cancer and other cancers in Asians (Qian et al. 2011). A correlation was also found between length of the allele and development of the disease. A study demonstrated that the risk of developing breast cancer increased in Iranian women carrying an allele longer than CA 19 and decreased in those carrying alleles shorter than 20, nevertheless this effect was more profund in women with both alleles longer than 19 (OD= 4.1; p = 0. 0002) (Javadi et al. 2012).

In a meta-analysis, Huang et al. (2011) observed no association between CA 17, 19 and 20 alleles and the risk of breast cancer, while two years later He et al. (2013) carried out a meta-analysis demonstrating that CA 19/19 alleles may provoke a decrease in the risk of developing breast cancer in Caucasian women, but not in Asian women.

In turn, SNP polymorphism and its combinations (haplotypes) among other genetic variations have been studied to investigate a possible association with breast cancer. The majority of SNPs studied are found in highly located areas known as Evolutionarily Conserved Regions (ECR) that are close to the transcription binding domains that provoke alterations in transcription regulation (Biong et al. 2010)

Increased mammographic density is considered one of the most important risk factors for the development of breast cancer (Harvey and Bovbjerg 2004, Boyd et al. 2005, Byrne et al. 2001). Around one-third of breast cancers occur in breasts with mammographic density greater than 50% (Ursin et al. 2005, Russo et al. 2005, Ziv et al. 2003) Mammographic density may be affected by body mass index, age, parity and also genetic variations in genes involved in the development of the breast, such as IGF-1 gene (Haiman et al. 2003, Tamimiet al. 2007) Diorio et al. (2005) found an association between mammographic density and IGF-1 serum in premenopausal women, although more recent studies have contradictory results (Rice et al. 2012, Rinaldi et al. 2014)

A study conducted with 964 postmenopausal women aimed at confirming correlations between mammographic density, SNP polymorphism, IGF-1 circulating levels and its binding protein, demonstrated only a common genetic association between IGF-1 haplotype, IGF-1 plasma levels and mammographic density in Norwegian postmenopausal women (Biong et al. 2010). Henningson et al. (2011) showed a relationship between SNP polymorphism, circulating IGF-1 levels and the risk of breast cancer. It was shown that neither a single SNP nor any diplotype (combination of two haplotypes) were associated with circulating IGF-1 levels in 325 Swedish women, and a rare diplotype variant was found to be significantly associated with a higher risk of developing breast cancer.

Another individual SNP (rs 7965399), located close to the transcription initiation site, more specifically at the 5' untranslated region of the IGF-1 gene has been associated with breast cancer risk in a recessive model, in which 403 Chinese women with breast cancer were recruited. This association became particularly more evident in patients who were menopausal before age 50 and in those who were estrogen-receptor negative (ER^-)

(OR=2.48; 95%CI: 1.08 – 5.67) and infiltrating ductal carcinoma (OR = 2.18; 95% CI: 1.08–4.38) (Qian et al. 2011).

The Breast and Prostate Cohort Consortium (BPC3), a collaboration of large North-American and European cohorts genotyped 1416 SNP for 24 gene variants involved in the IGF-1 pathway in 6,292 Caucasian postmenopausal women, diagnosed with breast cancer. A comparison between these women and 8135 women from the control group showed no significant association between SNPs and risk of breast cancer (P_{trend} 0.003–0.996) (Canzian et al. 2010). Another study that used BPC3 data, genotyped a total of 302 SNP Insulin-like Growth Factor (IGF) pathway genes in a sample of more than 5,500 Caucasian women and also failed to observe any association with breast cancer risk, but with a positive association of the SNP with the levels of circulating IGF, adjusted significance criteria (nominal p value < 2.1×10−4) (Gu et al. 2010).

Although a large number of studies have identified an association between IGF-1 gene polymorphism and breast cancer risk, few studies have investigated the relationship between these polymorphisms and disease progression. In analysis of the association between type CA-19 IGF-1 gene polymorphism in a breast cancer patient along with patient clinic pathological characteristics, as well as disease recurrence and survival, it was observed that homozygotes for non-19/non 19 CA alleles with non-metastatic breast cancer had favorable prognostic factors, a lower tumor recurrence rate (95% CI: 0.93-5.92, p = 0.06), longer disease-free interval (95%CI: 38.6–115.6) and longer survival (95% CI: 1.04-8.6, p = 0.03) (Yaren et al. 2012), while patients testing positive for human epidermal growth factor (HER2+) and carriers of the SNP (rs 2946834) allele have a worse prognosis (p = 0.020) and a reduction in disease-free survival (p = 0.027), probably due to increased levels of circulating IGF-1 (Muendlein et al. 2013). Thus, the reason behind the conflicting results between studies is still unknown but a possible explanation could be the variation in the ethnic composition of the study populations (Al-ajmi et al. 2012).

CONCLUSIONS

A growing number of studies support an association between IGF-1 gene polymorphism and breast cancer risk. However, conflicting results have been observed with different methodological approaches, distinct molecular subtypes studied, genetic differences between different populations and tumor heterogeneity. Therefore, elucidation of the patterns of IGF-1 gene expression may permit characterization of women at high-risk for breast cancer, as well as the development of strategies for early diagnosis and efficient treatment against the disease.

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