Review Article

Genetic polymorphisms, the metabolism of estrogens and breast cancer: a review

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Summary

Breast cancer is the most common female cancer and the second cause of cancer death in women. Despite recent breakthroughs, much of the etiology of this disease is unknown and the most important risk factor, i.e., exposure to endogenous and exogenous estrogen throughout life cannot explain the heterogeneity of prognosis nor clinical features of patients. Recently, many gene polymorphisms in the metabolism of breast cancer have been described as possible neoplasm etiologic factors. This review is an attempt to summarize the current knowledge about these polymorphisms and to determine new target genes for diagnosis and treatment of the disease. Polymorphisms in the genes *CYP17, CYP19, CYP1A1, CYP1A2, CYP1B1, UGT1A1, SULT1A1, 17-hydroxysteroid-dehydrogenase, COMT, GST, ESR1,* and *ESR2* are described.

Key words: Breast cancer; Metabolism of estrogens; Estrogen receptors; Polymorphisms; Metabolizing genes.

Introduction

Breast cancer is the most common female cancer and the second cause of cancer death in women. Despite recent breakthroughs in the knowledge of the molecular pathology of the disease, such as the discovery of mutations in the genes *BRCA1* and *2, p53* and *PTEN,* exposure to endogenous and exogenous estrogens throughout life still remains the most important risk factor accounting for the disease [1].

Clinical experience and most of the literature show great heterogeneity for susceptibility and prognosis of the disease, as well as a predilection for some families or populations, not fully explained by the risk factors mentioned earlier. Recent studies based on two large cohorts, the *Framingham Heart Study* [2] and the *Shanghai Breast Cancer Study* [3], suggest that gene polymorphisms influencing the estrogen metabolism pathway may play a key role in individual breast cancer risk.

Risk factors for breast cancer

Today, the most important risk factors for breast cancer include high serum estrogen levels, many ovulation cycles due to early menarche (younger than 12), or late menopause (older than 55), hormonal replacement therapy after menopause, use of oral estrogen contraceptives for ten years or more, and obesity after menopause (BMI > 30.7 kg/m^2) [4]. Obese women show higher serum estrogen levels due to greater estrogen biosynthesis and lower serum estrogen binding protein levels. However, they have longer menstrual cycles and, therefore, fewer ovulations, which may be protective before menopause.

Other risk factors are high bone and breast density (> 75% at mamography), as markers for high estrogenic action, nulliparity or first pregnancy older than 30 years, breast feeding for less than two years, BRCA 1 and 2 mutations and smoking habit [5]. Pregnancy and breast feeding are believed to induce the final ductal maturation, preventing malignant transformation.

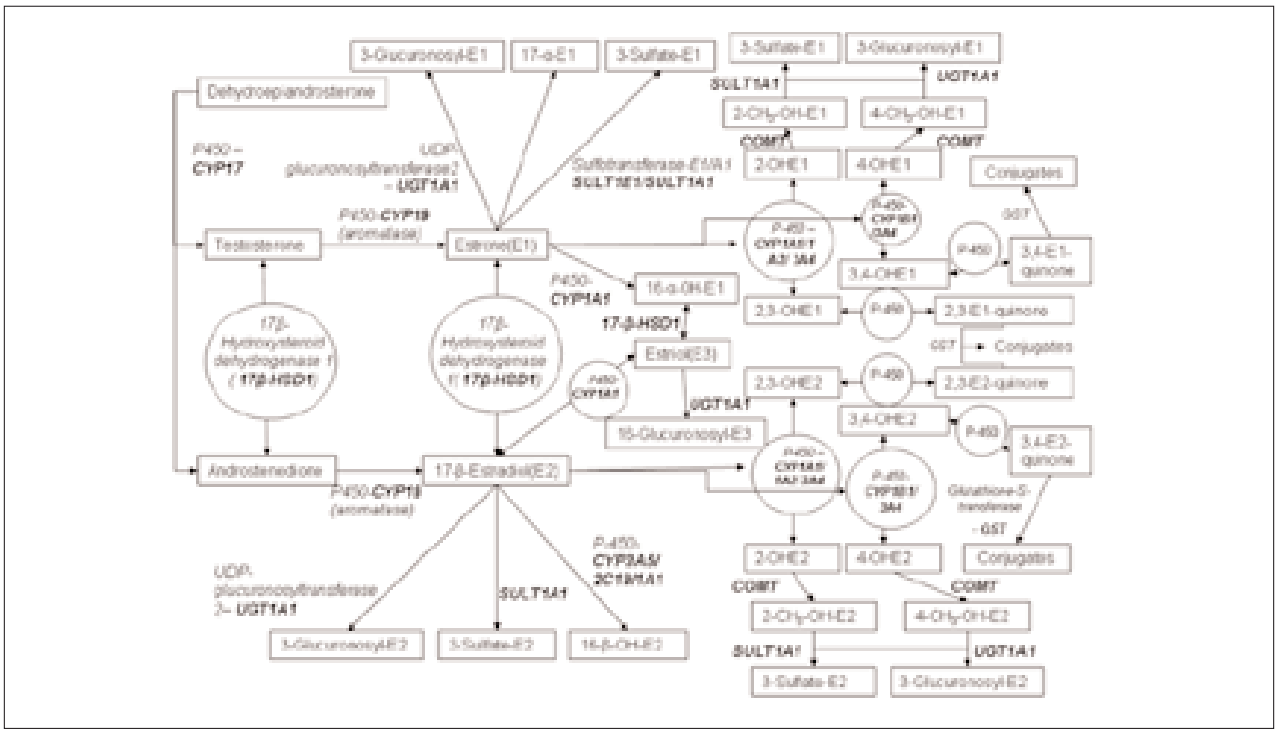
The prognostic factors currently used are surgical staging, nuclear and histological grades, and the expression of ESR1 and HER2. However, a recent review [6] has highlighted the importance of many genes that are related to the estrogen metabolism pathway and disease progression ("70-gene-profile"), as possible markers for breast cancer outcome.

Estrogen metabolism and action

The estrogen synthesis pathway is summarized in Figure 1. Dehydroepiandrosterone is produced in the adrenal glands and converted to testosterone and androstenedione by enzymes of the complex CYP17. They are further metabolized to estrone and estradiol by the enzyme aromatase (member of the complex CYP19) in the ovaries, during the first half of the ovulatory cycle, but also in the breasts, adipose tissue, liver, and muscles. The extragonadal production of these hormones is of major importance after menopause, when breast estrogen levels can be from 10 to 50 times the serum concentration [7]. Locally, in many tissues, estrone and estradiol can be converted to estriol by enzymes of the complex CYP1A1. Estrone, estradiol and estriol are interchangable due to the action of the enzyme 17-hydroxysteroid-dehydrogenase, and in the breast the action of estradiol predominates.

The primary metabolism of estrogens can follow two different pathways:

Revised manuscript accepted for publication October 1, 2007



1) Conjugation – Enzymes UDP-Glucuronosyltransferase 2 (UGT1A1) and Sulfotransferase-E1 or A1 (SULT1E1/SULT1A1) add the radicals glucuronil and sulfate, which are hydrosoluble to estrogens, and which are later excreted in the urine.

2) Hydroxilation – In the liver, breast and other tissues, enzymes related to the complex P450 promote the hydroxilation of estrogens, generating many compounds which will suffer secondary metabolism.

A) 16-α-hydroxyestrogens (16-α-OH-E1/E2) are normally produced in small amounts by enzymes in the complex CYP1A1 [7] and later glucuronized by the enzyme UGT1A1. One study [8] showed lower urinary levels of this product among women in Finland when compared to women from Asia, who have a risk up to three times lower for breast cancer. This suggests a possible protective action of 16-α-OH-E1/E2.

B) Catecholestrogens: 2-hydroxyestrogens and 4-hydroxyestrogens (2-OH-E1/E2 and 4-OH-E1/E2) – the main metabolites of estrogens [10] – are produced by the complexes CYP1A1, 1A2 and 3A4 (2-hydroxyestrogens) and CYP1B1 and 3A4 (4-hydroxyestrogens), and are methylated by the enzyme catechol-O-methyltransferase (COMT). The products from this reaction are conjugated to sulfate and glucuronil by the enzymes SULT1A1 and UGT1A1; 2-hydroxyestrogens are inactive and anti-angiogenic whereas 4-hydroxyestrogens have an estrogenic action even greater than estradiol and, after glucuronization, can cause damage to DNA. Therefore, a reduction in the 2-hydroxyestrogen/4-hydroxyestrogen ratio is related to a higher breast cancer risk [9].

C) Catecholestrogens: 2,3-hydroxyestrogens and 3,4-hydroxyestrogens (2,3-OH-E1/E2 and 3,4-OH-E1/E2) – the complexes CYP1A1, 1A2 and 3A4 can produce to a lesser degree, 2,3-hydroxyestrogens and the complexes CYP1B1 and 3A4, 3,4-hydroxyestrogens. These metabolites are oxidated by the complex P450, yielding quinones, which are later conjugated to glutatione by enzyme glutatione-S-transferase (GST). This process yields reactive oxygen intermediates which can damage DNA and the 3,4-hydroxyestrogens after this reaction can cause depurination [10].

Estrogens have a proliferative action and are responsible for breast and endometrium maturation, and maintenance of bone density. They act on two receptors, ESR1 and ESR2 (α and β), translated on different sites: *ESR1* in the long arm of chromosome 6 (6q25.1) and *ESR2* in the long arm of chromosome 14 (14q22-24). Both are intracellular receptors, with two binding-sites for estrogens (AF-1 and AF-2), sites for cofactors, and a binding-site for DNA. Structurally, they differ only in their binding site for estrogens, in which they show only 58% homology [11, 12]. After activation, they are dimerized and migrate to the cellular nucleus, binding to regulatory regions of DNA and activating the expression of transcription factors. There is some evidence that their activation also stimulates the transcription of mitochondrial DNA and the production of cAMP [7], TGF· and EDGF [9].

ESR1 is the most common in the whole body and responsible for the action of estrogens in the uterus, ovaries, endothelium and bones. ESR2 can be found in bones, cardiovascular epithelium, normal breasts, and ovaries [11].

Polymorphisms In Enzymes Related To Estrogen Metabolism And Their Role In Initiation And Progression Of Breast Cancer

CYP17

A polymorphism is a genetic variant that appears in at least 1% of the population.

The polymorphism A2 or MSP1 of this enzyme consists of a substitution of thymine (T) to cytosine (C) in the position 743572 in the promoting region of the gene. It is found in 32% of Asians, 22% of Japanese, 14% of Caucasians and 13% of Afro-Americans [13] and enhances the enzyme action, yielding higher levels of estrogens and androgens during childbearing ages [14-16], but lower levels after menopause [17]; these associations are stronger for Hispanics [16]. These findings support the theory that polymorphism enhances breast cancer risk, but one study [18] has related the alteration to a higher production of 2-hydroxyestrogen, which is anti-neoplastic.

In fact, some groups have related the polymorphism to a higher breast cancer risk for women in childbearing ages [19-23] and after menopause [24]. Others [14, 25-32], however did not find any relation at all, but discovered that polymorphism enhances the risk of hormonal replacement therapy [29] and lack of breastfeeding [30]. Studies in India found a higher risk for cancer [20, 24], but opposite results were reported in China [25, 32].

CYP19

The number of TTTA repeats in the intron 4 of the gene is polymorphic. Ten repeats have a prevalence of 8.2% in China [25], 6.3% in Russia [19] and 8.7% in Australia [33]. The polymorphism is said to influence gene splicing and stimulate a higher conversion of androgens to estrogens. In fact, one study [17] attributed this alteration to estradiol levels up to 21% higher than normal.

Many studies found no correlation between this polymorphism and breast cancer in China [25], England [33, 34] and the United States [35], however, others found a strong correlation with breast cancer risk [18, 19, 26, 36], size of the tumor [36] and family history of breast cancer [26]. In the latter, the polymorphism seemed to influence the risk for patients' daughters, regardless of the daughters' polymorphism, suggesting a role of intrauterine exposure to estrogen in the genesis of breast cancer.

CYP1A1

Four polymorphisms are known in this gene and the m1 (or Msp 1, or CYP1A1*2A) has a prevalence of 4.2% among Afro-Americans [37], 3.5% in Africa [38] and 38.3% in China [39]. The substitution of T for C in the position 3801, a noncoding region of the gene, is related to higher levels of 2-hydroxyestrogens [40], which in theory, reduces the risk of breast cancer.

In fact, there is a lower incidence of the disease in Chinese women bearing the polymorphism [41], nevertheless the same does not happen in Taiwan [42]. There is a higher risk for Afro-Americans [37] and Africans [38], but no relation for Indians [43] or Caucasians. Just one group [44] found a higher risk for earlier and higher grade cancer in Caucasians carrying the alteration.

CYP1A2

The polymorphism CYP1A2*F, a substitution of cytosine to adenine in position 167 of the promoter-region, is present in 67.3% of Canadians [45] and 68% of Europeans [46]. It is related to lower enzymatic activity and a higher 16-α-hydroxyestrogen/catecholestrogen ratio, which was associated with a lower breast cancer risk in one study [47], but not in others [48, 49].

CYP1B1

This gene is highly polymorphic and the polymorphisms m1 and m2 are of major importance. The m1 polymorphism is a substitution of valine to leucine in position 432 of the enzyme and can be encountered in 25% of Afro-Americas, 67% of Caucasians and 83% of Chinese [50]. The alteration is related to a higher production of 4-hydroxyestrogens, reducing the 2-hydroxyestrogen/4-hydroxyestrogen ratio [40] and enhancing the risk of breast cancer.

This risk was not statistically significant in many studies [51-55], but a meta-analysis found a higher risk for Caucasians [56] and women in Turkey with a BMI higher than 24 kg/m^2 [57]. However, no relation was found for the Chinese [56, 58] and even a reduction in risk was reported for Africans [56]. The risk seems to be directly proportional to age [56], but for cancers diagnosed after menopause, the polymorphism is related to a higher expression of ESR1 [51, 55] and better disease-free survival [59].

The m2, a substitution of asparagine for serine in the position 453, has a prevalence of 17.4% in Caucasians [51], 3.4% in Afro-Americans [51] and 29% in Europeans [54]. It enhances the enzymatic activity, reduces the levels of 2-hydroxyestrogens and 16-··-hydroxyestrogens, and rises the levels of 4-hydroxyestrogens [18], specially after menopause [55], which theoretically enhances breast cancer risk. In fact, one study [45] found a higher risk with family transmission, especially for women with a BMI higher than 27 kg/m^2, but it was not confirmed by other studies [51, 54, 55].

UGT1A1

The UGT1A1*28 is one extra TA repeat in the TATA-box in the promoting region of the gene and happens in 13% of the Chinese population [60]. In theory, it reduces enzymatic activity, lowers the estrogen inactivation ratio and enhances estrogen serum and tissue concentrations. In fact, carriers of the polymorphism have higher breast densities [61].

Two studies attributed the alteration to a higher risk, one in women with a family history of breast cancer [62], the other in young Chinese women without any family history, low BMI and late menarche [60], suggesting that in this population the alteration is a risk factor independent of estrogen levels. The polymorphism has also been associated with more aggressive tumors, a higher probability of being larger than 2 cm at diagnosis [62], and lower expression of estrogen receptors [63].

SULT1A1

The most common polymorphism in this gene is a substitution of G to A in codon 213, creating a substitution of arginine for histidine in the same position of the enzyme; 13.6% of Chinese [25], 50.2% of Europeans [64] and 41.6% of North-Americans [65] have an alteration related to an enzyme with half of its action [66].

Many studies found a higher risk for Chinese women [25, 67-69], smoking women in child-bearing ages [53] and after menopause [24]. All of them found similar risks, with an odds ratio of around 2.5. Moreover, the polymorphism has been related to a higher risk of lymph node metastasis [36, 64].

17-Hydroxysteroid-Dehydrogenase

The polymorphism B1 is a substitution of adenine to guanine in position 1954 (exon 6), generating a substitution of serine to glycine in position 312. Some studies attributed the polymorphism to a higher conversion of estrone to estradiol and a higher risk of breast cancer [70]. Afterwards, the risk was confirmed for obese women after menopause [32] and young women with normal BMI [22].

COMT

The polymorphism COMT-L is present in 27.4% of North-Americans [58], 25% of Caucasians [71] and 5.2% of Chinese [31]. A substitution of A to G, and the resulting substitution of valine for methionine in position 158, results in an enzymatic activity four times less and, consequently higher levels of 2-hydroxyestrogens [17, 18].

There are many studies assessing breast cancer risk regarding this alteration: one group [72] found a reduced risk, probably due to the anti-proliferative action of 2-hydroxyestrogens, while others attributed the polymorphism to a higher risk [31], both for fertile women [31, 72] and women after menopause [71], and some found no relation at all for women in China [58, 73], Europe [74, 75], Turkey [57] and North-America [76]. One study encountered a risk not related to age or hormone levels [74] and others found a risk influenced by BMI [72] and smoking habit [77].

In 2005, a meta-analysis [58] concluded that there was no relation between this polymorphism and breast cancer, but most of the eligible studies were conducted in Chinese women who have a lower risk of breast cancer.

GST

The polymorphism GSTM1 0/0 (null) inactivates the enzyme, allowing quinone conjugates to accumulate and damage the DNA. One study found a higher rate of somatic mutations in breast cancer tissues of women carrying the deletion [78] and two others attributed the alteration to a higher breast cancer risk [44, 79]. This, however, was not confirmed in a recent study conducted in Brazil [80].

ESR1

Four polymorphisms have been extensively studied in ESR1. The polymorphism PvuII is located in intron 1 and corresponds to the alteration c454-397C-T. It has been found in 35% of black women, 13% of Caucasians and 16% of Hispanics [81]. It is related to a higher estrogenic action, responsible for higher breast and bone density after menopause, higher serum cholesterol, earlier menarche [82] and menopause [83] and better response to hormonal replacement therapy [84].

Two groups [85, 86] found no association between the polymorphism and breast cancer, but others found a higher risk for ductal cancer for all ages [87], especially after menopause [83]. The risk seems to be directly proportional to BMI [83], to number of ovulation cycles and to serum estrogen binding protein levels [12]. One group has attributed the alteration to a lower probability of expressing progesterone receptors [86], but no influence in the expression of estrogen receptors [88].

The polymotphism Xbal, in intron 1, consists of the alteration c454-351A-G and occurs in 34% of the general population [83]. It is related to a better response to estrogens, later onset of menopause, and better breast density after hormonal replacement therapy [89].

There is a direct relation between the number of polymorphic alleles and risk for ductal cancer [83], but this relation is statistically significant only for women older than 45 years and after menopause [87]. The risk was confirmed for the Chinese [87] and Korean [85] populations, but not for women in Norway [90], Hispanics or Caucasians [91]. One study related the polymorphism to a higher expression of ERS1 in the tumor cells [86].

Allele 1 in codon 325 is the alteration CCC-CCG in exon 4 and has a prevalence in the general population of 55.4% [92]. The polymorphism leads to endogenous activation of the receptor [93], and is related to more aggressive ESR1-negative tumors [94]. What is more, it influences the action of ESR1 over the expression of e-cadherin, an adhesion molecule which regulates cell proliferation [95]. Two groups detected a higher breast cancer risk in women bearing this polymorphism, one analyzing the general population [96], while the other studied women with a family story of breast cancer [97]. One study related this SNP to a higher risk of lymph node metastasis [92], not confirmed by later studies [87, 96].

The multiple repetitions of GT in intron 1 of the gene ESR1 have been poorly analyzed. One group associated longer repetitions to higher breast cancer risks [98], and others related the alteration to higher mortalities among tumors expressing ESR1 [12, 84, 98]. Eighteen repetitions were associated with the highest mortality rates. All three studies are based on the Shanghai Breast Study database and found an interaction of this polymorphism and the polymorphisms PvuII e XbaI in breast cancer risk.

ESR2

During carcinogenesis breast tissue expresses higher levels of ESR1 and loses up to 60% of its ESR2 expression [99]. This led to the theory that ESR2 may control the mitogenic action of ESR1 [100].

The effect of polymorphisms in this gene on breast cancer is poorly understood. In China, two alterations have been described: C(14206)T and C(33390)G, in intron 5 and exon 7, respectively. In a case-control study with 1,134 cases and 1,235 controls [12], the polymorphism C(33390)G was strongly associated to breast cancer, with an odds ratio of 2.5, which could be as high as 4 for women with high estrogen and low estrogen-binding protein levels. The alteration C(14206)T has been associated to a higher incidence of benign fibroadenoma.

Two groups have recently evaluated the association of the number of CA repeats in the gene and breast cancer risk in Caucasians. One of them found out that shorter repetitions are an independent risk factor [101], while the other found a significant risk only when the repeats were associated with other alterations in ESR1 and the androgen receptor [102].

Conclusion

The evaluation of gene polymorphisms must be cautious. The heterogeneous distribution in populations make it very difficult in study comparisons carried out in different countries. Furthermore, the change of function promoted by the alteration is much more minimal and, if the impact of a polymorphism seams huge, the presence of confounding factors should be considered.

Analyzing risk factors for neoplasms is also difficult. The disease is multifactorial and many of these factors are unknown and vary in different populations.

For this reason, there are polymorphisms that, in theory, are related to higher breast cancer risk, but their prevalence in the population is so high that they are unlikely to be independent risk factors. For example, the polymorphism m1 of the gene CYP1B1 has been associated to a higher breast cancer risk in Caucasians by two meta-analyses [56, 57], and can be found in up to 65% of this population [50]. There are also polymorphisms related to a higher risk in some populations, but not in others, like the same CYP1B1, which was not related to breast cancer in the Chinese population, despite being present in 83% of this population [56, 58]. This difference is certainly due to other factors affecting the gene-gene and gene-environment interaction.

However, there is enough evidence to conclude that polymorphisms affecting the metabolism and action of estrogens play important roles in breast cancer. Based on the data presented in this article, we suggest the following associations of polymorphisms and breast cancer, which must be confirmed by proper studies:

– *Probably associated with breast cancer:* UGT1A1*28, SULT1A1 Arg213His.

– *Association only for some populations*: CYP17A2, CYP1A1m1, CYP1B1m1, ESR1 XbaI.

– *Probably not associated with breast cancer:* COMT-L

– *Insufficient data:* CYP19(TTTA)n, 17β–Hydroxysteroid-dehyirogenase-B1, CYP1A2*F, CYP1B1m2, GSTM1 (null), ESR1 325 (CCC-CCG), ESR 1 PvuII, ESR1 (GT)n, ESR2 C(33390)G, ESR2 (CA)n.

When analyzing the prevalence of polymorphisms in different populations, it becomes clear that the polymorphism SULT1A1 Arg213His, probably associated with breast cancer, is less common in the Chinese, who have a reduced breast cancer risk, and the ESR1 PvuII, also related to a higher risk, is more common in black women, who have higher incidences of the disease. These findings do not fully explain the different incidence of the disease in these two groups, but suggest that it may be related to gene polymorphisms.

A more careful analysis of the polymorphisms presented here and the discovery of new ones may detect new factors influencing breast cancer risk and prognosis, with an important impact on the diagnosis and treatment of the disease.

Acknowledgments

We would like to thank Anderson Luis do Nascimento and the gynecologist Ismael Dale Cotrim Guerreiro da Silva for their assistance.

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