Original Article

Incidences and Etiology of Breast Cancer, on the basis of CYP450 Genes Polymorphisms

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Abstract

Breast carcinoma is the most predominant malignancy in women and stands as the second leading (15%) of cancer death amongst females. Breast cancer is one-fourth of female cancer cases worldwide with 200,000 cases in the United States of America which includes twenty-seven percent of all cancers in females; 320,000 cases in Europe which include thirty-one percent of all cancers in females. It is the 2nd reason for death among Iranian females, and one million new cases are diagnosed worldwide annually. Breast cancer accounted for twenty-six percent of all female cancers with a crude incidence rate of twenty-three percent in 100 thousand in Tehran province. During the last four decades, its enhancing incidence rate has made breast cancer one of the most dominant malignancies among Iranian women. In a descriptive cross-sectional investigation, a four-year period medical existing data associated with the pathology center in Tehran were evaluated. Data were extracted and clinical and other variables were contrasted between benign and malignant lesions. Findings revealed that the mean (± standard deviation) age was forty-two years. In four hundred cases (36%) the lesions were malignant and in seven hundred cases (64%) those were benign. The most common kinds of benign lesions were fibrocystic modifications (43%) and Adenofibroma (28%) and the most prevalent malignancy was invasive ductal carcinoma (88%). In this review article, incidences and etiology of breast cancer risks on the basis of CYP450 genes polymorphisms have been investigated.

Keywords: Breast Cancer, Genes Polymorphism, Pharmacology

Introduction

Breast cancer is generated in the cells of the breasts. After skin cancer, breast cancer is the most prevalent cancer identified in females in the United States. Breast cancer can be seen in both males and females, but it's far more prevalent in females. Prophylactic mastectomy is utilized to decrease the incidence of breast cancer in women with genetic predisposition and family history of breast cancer, and the rate of application is enhanced nowadays.

The National Cancer Institute guesstimates that the cost of breast cancer care will reach $20 billion in the U.S. in 2020. It is assessed in Iran and other countries that the annual occurrence of cancer in the world will increase from 14 million in 2012 to 25 million in 2030, of which more than seventy percent happens particularly in developing countries. Breast carcinoma is still the main health issue in many developed countries [1]. Breast carcinoma incidence rates are enhancing quickly in women 50 and older. In the 2000s because of the enhanced detection of smaller, earlier-stage cancers with the widespread adoption of the screening of mammography among asymptomatic women, counts for 22–28% of malignant tumors in women with an annual incidence of about 900–1100 cases, with one million new cases diagnosed in the world annually. Breast cancer is without a doubt the most prevalent female cancer, including about 21% of all new cancers in women. The highest age-adjusted incidence rate is stated for North America, being eghty-seven per 100 thousand women per year, while the lowest rate noted in China. Breast cancer follows a sharply enhancing age gradient up to forty years of age, after which the rate of enhancement slows down. Even though, there are three times as many new cases diagnosed annually as in the late 1990s, breast cancer mortality has remained largely unaffected. This may at least partly be clarified by earlier detection of the disease because of efficient screening programs and accessibility of improved remedies. The highest annual mortality rates for breast cancer are reported

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for the UK, the Netherlands and Denmark, being over 25 per 100 thousand in these countries [2]. The high rates of breast cancer occurrence and mortality is noted in industrialized Western nations and lower rates for less industrialized and Asian nations, disparate breast cancer incidence rates among American Caucasians. Enhanced estrogen levels are a known risk factor for breast cancer. They can result from differences in the enzymatic machinery responsible for estrogen metabolism, a reason why functional polymorphisms of enzymes involved in estrogen biosynthesis and catabolism may contribute to this risk. Up to now, conflicting findings have been reported from association investigations [3].

Incidence and Frequency in Iran

Breast cancer is accounted for twenty-six percent of all female cancers with a crude incidence rate of twenty-three percent per 100 thousand in Tehran in 2010. Two screening programs and a cross-sectional investigation revealed that the prevalence rate of breast cancer was three hundred and fifty-two per 100 thousand women aged thirty to sixty-five in Bushehr in 2010, six hundred and sixty per 100 thousand for females thirty-five years and older in Shiraz in 2011 [4], and one hundred and fifty per 100 thousand for females aged thirty years and over in Northwest of Tabriz. The incidence rates in Iran, similar to other Asian countries, during the last four decades, have been enhanced, making the breast cancer one of the most frequent malignancies among Iranian females. In a descriptive cross-sectional investigation, a four-year period medical existing data associated with the pathology center in Tehran were evaluated. Data were extracted and clinical and other variables were contrasted between benign and malignant lesions. The findings revealed that the mean (± standard deviation) age was 42 years. In 400 cases (thirty-six percent), the lesions were malignant, and in 700 cases (sixty-four percent) those were benign. The most prevalent sorts of benign lesions were fibrocystic changes (43%) and Adenofibroma (28%) and the most frequent malignancy was invasive ductal carcinoma (88%). The lesions were left-sided, right-sided, and bilateral in fifty-one, forty-three, and six percent, respectively [5].

The mean lesion size was 2.3 (1.32) centimeters. The age, side of the lesion, and gender were related to malignancy (P=0.01) and size was not related to the type of lesion (P>0.05). According to the obtained results in this study, it may be concluded that general characteristics and related factors of benign lesions in Iranian patients are similar to other worldwide reports. 298 patients with breast cancer were reported in 2014 and 380 cases in 2016 in Mazandaran province. The crude occurrence rate of breast cancer among the females in Mazandaran province was 17.45 and 16.32 per thousand in 2014 and 2016, respectively [6]. The ASR rates of breast cancer were twenty-seven and twenty-five per hundred thousand in the investigated periods, respectively. Most cases happened in women aged 49-55 years (twenty-one percent, annual rate). The most prevalent kind of breast cancer morphology in 2014 and 2016 was ductal carcinoma. Breast cancer has an impact on Iranian females at least ten years younger than their counterparts in developed countries. The death rate of breast cancer was 5.8 per 100,000 females in Tehran in 2008, 2.5 per 100,000 for the female population, and 13236 life lost in the eighteen provinces of Iran in 2011. Developing countries hope to be on the threshold of eradicating breast cancer as a key public health hazard. Early discovery of breast cancer remains an essential concern to health specialists. On the basis of the World Health Organization's approvals complementing national cancer control programs, evaluation of the magnitude of the cancer issue (i.e., incidence, prevalence, and mortality) is the first step in this procedure. There are numerous published investigations about breast cancer in Iran, but the epidemiological sides of Iranian breast cancer are ambiguous [7].

Etiology of breast cancer

The etiology of breast carcinoma is still inadequately understood in spite of known breast carcinoma risk factors such as age, gender, ethnic origin, reproductive events (pregnancy, menarche, breastfeeding, menopause) like delayed childbearing and having fewer children (increased life expectancy), early age at menarche, and late age at menopause, estrogens, exogenous hormones (hormone replacement therapy and oral contraceptives), lifestyle and environmental risk factors (pollution, alcohol, diet, obesity, chemicals), ionizing radiation, chemopreventive agents, as well as genetic factors (highland and low penetrance breast cancer susceptibility genes). High body mass index (BMI) and perhaps low physical exercise are also risk factors of postmenopausal breast cancer, acting via interference with hormonal levels. Compared with sporadic breast cancer, which has an estimated incidence frequency ranging from 89% to 96%, familial breast cancer has been estimated to occur only at 5% to 12% frequency. Nevertheless, the most frequently characterized predisposing factor for the disease is positive family history [8]. Interestingly, less than 12% of breast cancer types are attributable to a single highly penetrant inherited predisposing allele. Less than a quarter of familial risk factors have been connected to mutations in identified breast cancer genes. Mutations in highly penetrant genes in inherited breast carcinoma such as BRCA1 or BRCA2 confer a comparatively high risk for developing breast carcinoma, though this risk accounts only for about six to twelve of all breast carcinoma cases. It is suggested that the impact of low penetrance cancer susceptibility genes controlled by environmental contact and lifestyle factors are probable to account for most of sporadic breast carcinoma cases. Also, the role of reactive oxygen species (ROS) has been associated with the etiology of cancer, as they are known to be mitogen to a variety of cells, and consequently capable of tumor promotion. Recent investigations have provided significant new insights into the molecular epidemiology and genetics of breast cancer [9].

Much of this research has focused on the aggregation of breast (and ovarian) cancer within high-risk families, as well as on the starring role of key cancer susceptibility genes, such as BRCA2, BRCA1, andp53 germ-line mutations. Presumed relationships, such as that between heterozygosity for ATM (a gene mutated in ataxia telangiectasia) and the danger of breast cancer, have also been reviewed. These susceptibility genes account for less than five to ten percent of breast cancer cases in the population. Nevertheless, it is commonly evidenced that the beginning of breast cancer is a result of cumulative genetic injuries resulting in genetic modifications that consequence in the inactivation of tumor suppressor genes and stimulation of proto-oncogenes. These sequentially are followed by unrestrained cellular multiplying and/or aberrant programmed cell death, or apoptosis [10]. Other genetic factors may have superior public health significance. The existence of low-penetrance genetic polymorphisms could explain why some females are more sensitive than others to environmental carcinogens such as replacement estrogens. For instance, genetic polymorphisms for cytochrome P-450 enzymes and N-acetyltransferase, have been surveyed concerning cigarette smoking and breast cancer susceptibility in women. Or CYP17 is an agent that codes for a cytochrome P-450 enzyme involved in the metabolism of estrogen, has been related to a young age first menstruation and enhanced risk of breast cancer. Genetic polymorphisms could be linked with breast cancer. Most of the threat factors for breast cancer are associated with long-lasted or enhanced contact with estrogen [11]. The key impact of estrogens is believed to be by means of the motivation of breast-cell proliferation, in this manner enhancing the chances that a cell bearing a potentially cancer-causing mutation will proliferate. They are for that reason considered to account for a high quantity of breast cancer cases. The etiology of breast cancer in younger and older females may vary in terms of inheritance, carcinogenesis, and prognosis, signifying alterations in the biological source of the disease. Inherited mutations in genes with an autosomal dominant pattern and high penetrance have been severely related to early onset breast carcinomas. Xeno-estrogens, which comprise dyes, pesticides, pollutants, plasticizers, and food preservatives that have estrogen-like influences, have been recommended to have a title role in the etiology of breast cancer. Xeno-estrogens have also been named endocrine disrupters as they interfere with the activities of endogenous estrogens. For instance, catechol metabolites of polychlorinated biphenyls (PCBs) have been recommended to modify estrogen metabolism by stopping the inactivation of carcinogenic estrogen metabolites. A recent comprehensive review of DDT and DDE did not, though, back the relationship between these compounds and breast cancer risk. In premenopausal non-pregnant females, nearly all estrogen is of ovarian source, while after menopause most estrogen is produced by aromatization of androstenedione to estrogen in peripheral adipose tissue. The xenobiotic-metabolizing enzymes (XME) gene polymorphisms may consequently describe subpopulations of women with higher lifetime exposure to metabolites, estrogens, and other carcinogens' person-to-person dissimilarities are essentially attributed to polymorphism in the genes encoding for the XMEs [12]. Such dissimilarity could clarify a portion of the breast cancer susceptibility associated with reproductive events and hormone exposure, as well as the other lifestyle/environmental risk factors.

Cytochrome P-450 Enzymes associated with breast cancer

These enzymes have a very broad substrate specificity including environmental toxins, therapeutic drugs, and various groups of endogenous composites, including steroid hormones, eicosanoids, and retinoid. Thus, this group of enzymes is implicated in several different biological processes including carcinogenesis, determining response to drugs, and cell signaling. In the metabolism of xenobiotic (foreign) chemicals, cytochrome P450s or monooxygenases conducts a significant function by catalyzing the hydroxylation reaction. In this report, we review the investigation on genetic polymorphisms of CYP450 enzymes that may have an etiological title role in breast cancer [13]. Cytochrome P450 enzymes composed a multi-gene "superfamily" that plays an essential role in steroidogenesis and activation or detoxification of environmental chemicals such as polycyclic aromatic hydrocarbons, arylamines, benzo (a) pyrene, and heterocyclic amines as well as endobiotics. Generally, the objective of xenobiotic metabolism is to enhance the water solubility of numerous foreign chemicals to eradicate them from our physiological system; and this process happens in two phases. Cytochrome P450 enzymes are involved in phase I reaction, which sometimes transforms biologically inactive compounds into active or toxic metabolites. In this investigation, a comprehensive examination was performed into the expression of a wide range of cytochrome P450s in breast cancer [14].

Biosynthesis and Metabolism of estrogens

Biosynthesis of estrogens includes a series of enzymatic steps from cholesterol to C-19 androgens and C-18 estrogens. In the biosynthesis of estrogen CYP17, CYP11A, and CYP19 are principally essential (Fig. 1). CYP19 catalysis the ultimate steps from androgens to estrogens undergo extensive oxidative metabolism via the action of several CYPs. Numerous cytochrome P450 enzymes are identified in normal as well as cancerous breast tissues such as CYP1B1, CYP2C9, CYP1A1, CYP2B6, CYP2A6, CYP2E1, and CYP3A4. Although phase I enzymes for instance CYP2C6, CYP1A2, and CYP3A4 are involved in hepatic and extrahepatic estrogen oxidation, CYP1A1 and CYP1B1 exhibit their leading expression in breast tissue. The cleavage of the side chain of cholesterol by CYP11A to form pregnenolone and progesterone (C-21 steroids) is a rate-limiting step in the biosynthesis of all steroids. Hydroxylation and subsequent cleavage of the C-21 steroids by CYP17 yields C-19 steroids, dehydroepi, and rostenedione [15].

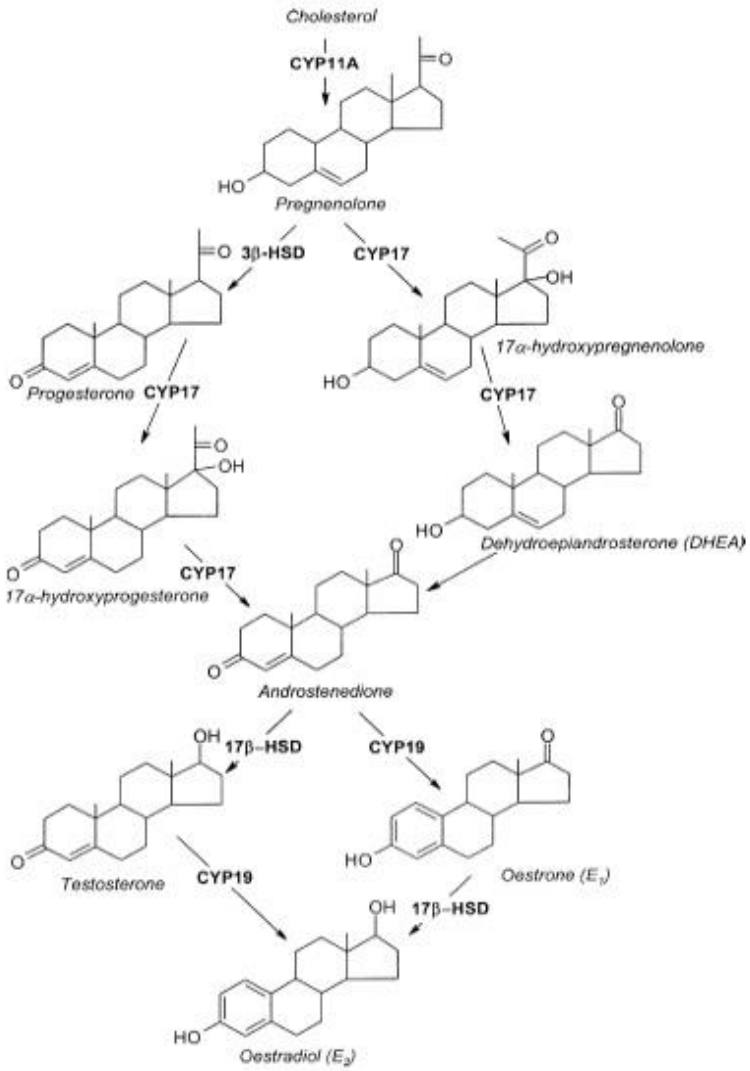

Fig. 1. Biosynthesis of estrogen from cholesterol

CYP450 Enzymes involved in the synthesis of estrogens

CYP11A1

In a study, the TAAAA repeat polymorphism next to the promoter of the CYP11A gene was believed to be a possible imperative susceptibility factor for breast cancer threat. CYP11A1 gene is comprised of nine exons covering 29,834 chromosome 15q24.1, which harbors extra P450 genes. The cholesterol side-chain cleavage enzyme (P450scc), encoded by the CYP11A gene, catalyzes the transformation of cholesterol to Pregnenolone. This is the initial and rate-restraining phase for the biosynthesis of all steroid hormones (progesterone, estrogens, and androgens). The positive relationship between CYP11A genotypes and breast cancer threat was witnessed in both pre- and postmenopausal females [16].

CYP1A2

A number of polymorphisms in the CYP1A2 gene have been defined, most of them with imprecise functional prominence. No obvious connotation of the CYP1A2*1F polymorphism with breast cancer danger was established in nonsmoking Chinese females in a research, though it cannot be ruled out that other CYP1A2 polymorphisms may have an impact on the risk of breast cancer. Cytochrome P4501A2 (CYP1A2) is situated on chromosome 15q22-qter. CYP1A2 catalyzes metabolic activation of a diversity of aryl- and heterocyclic amines such as 2-aminoanthracene and 2- acetylaminofluorene. It also catalyzes the activation of PAHdiols to reactive metabolites at much gentler rates than CYP1A1 and 1B1. It also oxidizes other xenobiotic substances including theophylline, 7-ethoxyresorufi n, acetaminophen, phenacetin, caffeine, antipyrine, lidocaine, and R-warfarin. This is one of the leading enzymes that catalyze 2-hydroxylation. The result is in accordance with a valueless relationship between this polymorphism and ovarian cancer [17].

CYP17

To assess the significance of CYP17 gene polymorphism in the early onset of breast cancer, frequencies of the 2 CYP17 alleles were evaluated in a group of young consecutive breast cancer patients and a healthy female control population. The CYP17 gene, situated on chromosome 10q, encodes the cytochrome P450c 17 enzyme, which in women is principally expressed in the ovary and adrenal cortex (Fig. 2). It intervenes both steroid 17-hydroxylase and 17,20-lyase activities, and catalyzes a rate-restraining stage in sex steroid synthesis resulting in the dehydroepi, precursor, and rosterone. The protective influence of later age at menarche was only witnessed among women without the A2 allele, though, proposing a likely interactive influence with CYP17 genotype [18]. Potential explanations for these varying results across researches include dissimilarities in underlying racial distributions and variances in breast cancer stage at diagnosis. Other investigations indicated the correlation between genotype and diverse tumor features. In the CYP17 gene influences the early onset of breast cancer by enhancing the risk of the illness in individuals carrying the A2 allele.

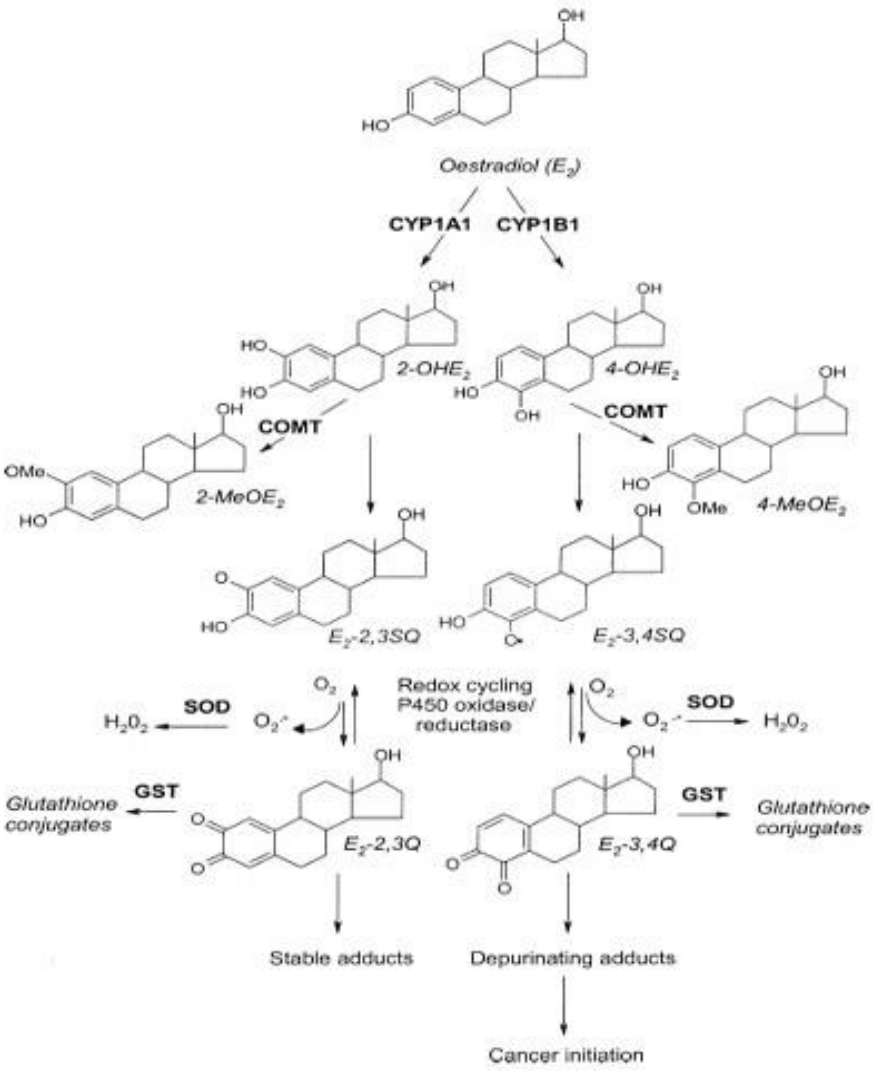

Fig. 2. Metabolism of estrogen

CYP19

The CYP19 gene positioned on chromosome 15q encodes steroid aromatase that catalyzes the transformation of C-19 androgens to estrogens. Oppositely, another polymorphism (Figure 3) in the CYP19 gene, giving rise to the amino acid substitution Arg264Cys has also been investigated in correlation with breast cancer risk, but seems to have no influence in this context. Nor has it been stated to modify the catalytic affinity of the enzyme. Estrogen is predominantly circulating in postmenopausal women as estrogen, derived from the peripheral aromatization of androstenedione. Trinucleotide repeat polymorphism [TTTA]n in CYP19 gene, which has been investigated in correlation with breast cancer risk, could modify the mRNA splicing site [19].

CYP19A1

The current meta-analysis recommends that, to approve the risk recognized in the present meta-analysis, three variants (rs700519, rs10046, and rs2236722) with a larger sample size of diverse ethnic populations will be required. CYP19A1 gene is situated on chromosome 15q21.2 regions and encodes aromatase, which transforms androstenedione and testosterone into estrogen and estradiol, respectively. aromatase activity can be modified by CYP19A1 mutations, which influences estrogen levels indirectly, and may eventually modify susceptibility to breast cancer. CYP19A1 is a significant estrogen biosynthesis enzyme and plays an imperative role in the development of breast cancer [20].

CYP21

The gene encoding 21-hydroxylase (CYP21) is responsible for the 21-hydroxylase activity, and this recommends that CYP21 may play a starring role in hormone-dependent tumors. Cytochrome P450 21 (CYP21) is situated on 6p21. A relationship of the CYP21*15 allele with polycystic ovary syndrome was stated in 32 hyperandrogenic patients. No statistically significant association of CYP21 genotypes was identified with regard to adrenocortical tumors in a study involving Swedish 27 patients [21].

Table 1. Polymorphic enzymes involved in estrogen synthesis with a likely role in breast cancer risk [22]

	Gene	Chromosomal localisation	Polymorphism	Breast cancer risk OR (95% CI)
P450scc (CYP11α)	CYP11A1	15q22.3	$(TTTTA)_n$ 5' UTR	?
Cytochrome P450c17 α	CYP17	10	T > C 5'UTR	OR 2.5 (1.07-5.94) no increased risk
Cytochrome P45019C	CYP19	15q21	G > A 5'UTR	?
(aromatase)			C > T 5'UTR	?
			G > A exon 3	?
			TTTAn intron 4	OR 2.42 (1.03-5.80)
			G > T intron 5	?
			T > A intron 6	?
			C > T exon 7	No increased risk
			C > T intron	?
			T > C 3'UTR	OR 1.53 (1.04-2.16)
			G > T 3'UTR	?
			T > C 3'UTR	?
17β- Hydroxysterid dehydrogenase	17β-HSD	17q21	5'UTR deletion of 12 bp	?
			5'UTR (AAAAT)2	?
			9936A > G	OR 1.52 (0.97-2.38)
			29342C > T	?
Steroid sulphatase	STS	Xp22.3	NCoI	?
				?
P4501A1	CYP1A1	15q23	6235T > C	RR 1.05 (0.74-1.50)
			4889A > G	RR 0.88 (0.58-1.33)
			4887C > A	
P4501B1	CYP1B1	2p21	1294G > C	OR 0.7 (0.4-1.5)
			1358A > G	OR 1.3 (0.3-4.8)

CYP1A1

The CYP1A1 has been investigated as the principal enzyme triggering cigarette smoke constituents and other environmental pollutants such as PAHs resulting in carcinogenic electrophilic molecules. The latter modification has been stated to cause lower catalytic activity against progesterone. CYP1A1 (AHH Gene) is located on chromosome 15q and codes for AHH2 (Fig 2) (Table 2) [22]. AHH metabolizes polycyclic aromatic hydrocarbons and has been witnessed in breast tumor tissue. AHH is strongly inducible, i.e., it exhibits greater enzymatic activity with increasing exposure to substrates. The CYP1A1 4 allele was recently revealed to be correlated with enhanced breast cancer risk among French-Canadian women, particularly among postmenopausal women. While no noteworthy overall correlation between breast cancer risk and CYP1A1 ∗2A or CYP1A1 ∗2C alleles have been indicated in Caucasian investigations, meaningfully greater risks have been revealed for women with early onset of smoking and

the CYP1A1 ∗2A allele, for those who had smoked as well as CYP1B1.

CYP1B1

It was stated that subjects with homozygous mutant genotypes at codon 432 have an enhanced percentage of tumors with receptors for estrogens and progesterone. Additional investigations are mandatory to detect correlations between subtypes of breast cancer. In spite of these negative findings, still, a role for CYP1B1 gene polymorphism on breast cancer susceptibility may exist. As 4-hydroxylated metabolites signify only a minor portion of total urine estrogens, it was formerly considered as a minor path for metabolism. However, CYP1B1 is present virtually in all adult and fetal tissues with high levels found in the breast. CYP1B1, the gene of which is situated at 2p, seems to be the key CYP450 enzyme responsible for the 4-hydroxylation of estradiol (Figure 4), but also triggers many PAHs and carbylamines. Likewise, as it is co-localized with CYP19, the enzyme-producing estrogen, this could result in the high local fabrication of possibly carcinogenic estrogen metabolites [23].

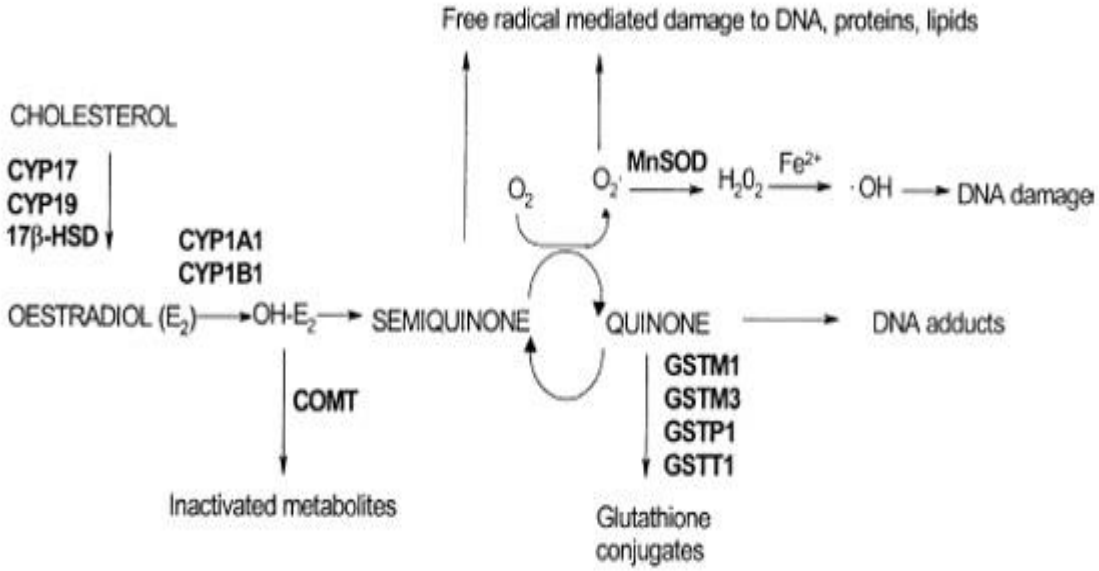

Fig. 3. Schematic of enzymes with known polymorphism

CYP2D6 (Debrisoquine Hydroxylase Gene)

The CYP2D6 gene is situated on chromosome 22q and codes for debrisoquine hydroxylase. Comparable to other polymorphically expressed P-450 enzymes (Table 1), the CYP2D6 gene may possibly activate procarcinogens or, contrariwise, detoxify carcinogens. Extra carcinogens will be metabolized to their genotoxic metabolites by means of wild homozygous CYP2D6 genotype. Subsequently, this superior enzyme activity most likely enhances DNA injury levels and accordingly the risk of breast carcinoma. Nonetheless, subjects carrying two copies of the CYP2D6 wild type allele have greater enzyme activity than those with one or no copy of the wild type allele [24].

CYP3A4

Early adolescence and the interval until menarche (when the breast is vulnerable to environmental carcinogens) may be a serious period in breast development. Consequently, it would be of importance to examine whether the CYP3A4*1B and CYP3A phenotypes are threat factors for breast cancer. The CYP3A4 gene, which is 27,592 bps and has thirteen exons, is sited on chromosome 7q21.3-q22.1. CYP3A4 and CYP3A5 are the major enzymes responsible for drug metabolism in adults. The promoter region encompasses a basal transcription element (–35 to–50). Subsequently, a disproportionate drop in testosterone levels may be possibly caused by high-activity CYP3A4*1B, which may enhance the estradiol-testosterone ratio and lead to the hormonal cascade that accompanies puberty (luteinizing hormone/follicle-stimulating) hormone ratio enhancement, hyper plasticity insulin secretion, luteinizing hormone, enhancement in BMI). In the 5′untranslated region (UTR) there are an AP-3 binding site, a p53 binding motif, a specific DNA sequence to which the protein p53 can attach, a hepatocyte nuclear factor-4 element, two hepatocytes nuclear factor-5elements, a glucocorticoid response element, and an estrogen response element. CYP3A4 is the most essential CYP in human hepatic tissue and involves in testosterone metabolism, catalyzing its 6_2_, and 15_ hydroxylation. A hypothesis that could explain these findings is that CYP3A4 leads to modifications in the estradiol: testosterone ratio as these hormone levels rise at the onset of puberty [25]. Like estradiol, serum testosterone concentrations in prepubertal girls are meaningfully lesser than those in pubertal girls.

CYP3A5

Up-to-date research found that expression of CYP3A4/5 was meaningfully associated with lymph node metastases in breast carcinoma. CYP3A5 is nested on chromosome band

7q21-q22.1. Known coding alleles include CYP3A5*2, *4, *6, *7, *8, *9, and*10 that are present in different exons, especially exons 7 and 11. Further, interionic single nucleotide polymorphisms (SNPs) likewise is existent. Cytochrome P450 3A5 (CYP3A5) in humans is involved in the 16α-hydroxylation of estrogens. As 16-hydroxy-estrogen 1 (16-OHE1) is a presumed breast carcinogen, understanding of the enzymes involved in its synthesis offers a foundation for blocking its synthesis in vivo. CYP3A4 and CYP3A5 are both expressed in human female breast tissue, but not in all people; these findings also offer a base for the choice of possibly susceptible subjects.

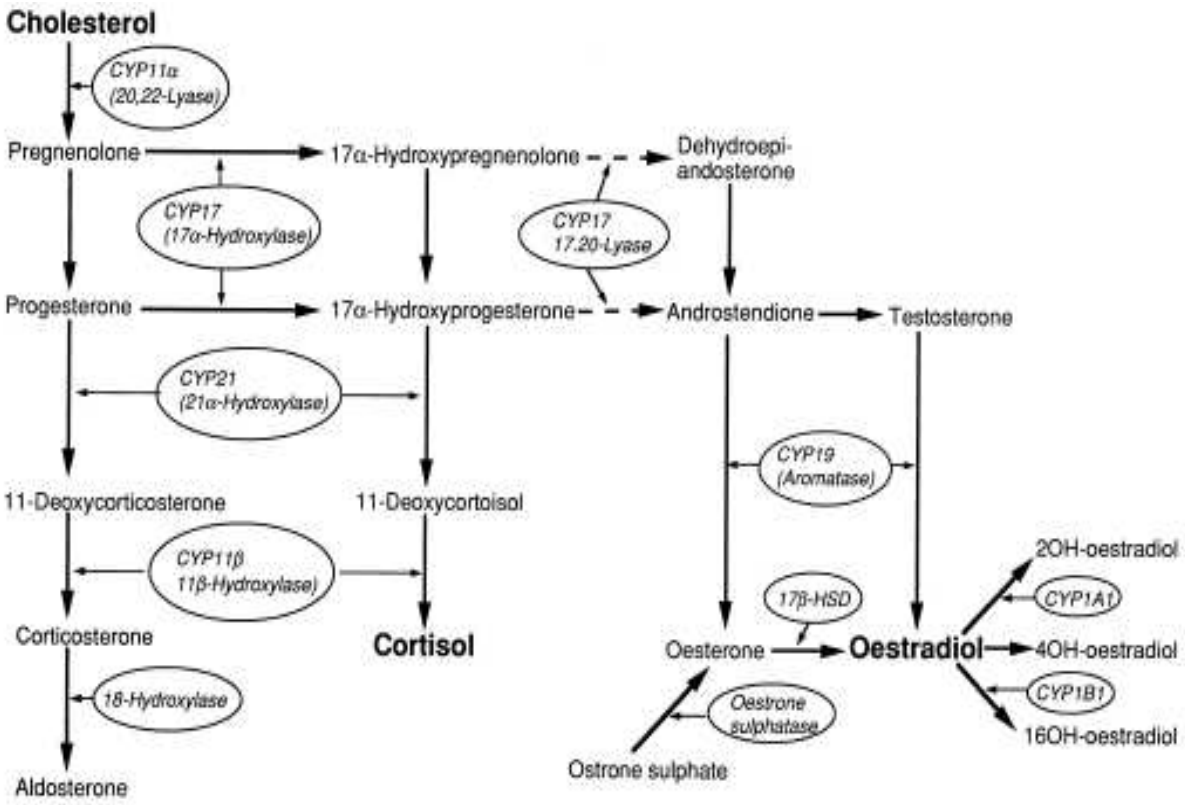

Fig. 4. The estradiol synthesis metabolic pathway

CYP2C19

This enzyme catalyzes the 17 beta-hydroxyl dehydrogenation and 16 alpha-hydroxylation of estradiol. All the same, not much afford has been made hitherto to discover an imaginable relationship between CYP2C19 polymorphisms and breast cancer risk. Arachidonic acid is transformed to EETs by Cytochrome P450 epoxygenases. Some of the EETs are reported to have potential ant migratory, antioxidant, and anti-apoptotic effects, and these effects help to explain the association of CYP2C19 with the mechanism of breast cancer. Both of the last two groups explored the association of CYP2C19 genetic polymorphisms with breast cancer in European subjects. Conversely, both CYP2C19*17 (CYP2C19_-806_C>T, rs12248560) and CYP2C19*2 (CYP2C19_681_G>A, rs4244285) are infrequent in the Chinese population unity. CYP3A4⁄5 and CYP1B1 were meaningfully correlated with lymph node metastases and poor tumor differentiation, respectively. Numerous investigations have reported dissimilar conclusions for the association with CYP2C19. It is stated that CYP2C19*2 but not CYP2C19*3 polymorphism is correlated with enhanced survival in breast cancer patients utilizing tamoxifen. Justenhoven et al.[14] recommended CYP2C19*17 but not CYP2C19*3 and CYP2C19*2 is correlated with reduced breast cancer risk.

CYP2C8/9

Numerous genetic polymorphisms in genes such as (CYP)2C8, cytochrome-P450, and CYP2C9, could affect survival after a cancer diagnosis because of their role in the metabolism of various breast cancer drugs, including tamoxifen and chemotherapy. In vitro investigations have revealed that overexpression of CYP2C9 elicits angiogenesis via activation of the epidermal growth factor receptor (EGFR). Functional polymorphisms of CYP2C8 and CYP2C9 may thus be of importance for breast cancer risk, tumor characteristics, and treatment response (Table 2) [26].

Table 2. Estrogen Biosynthesis related P450 enzymes

Enzyme	Function	Steps of catalysis	Xenobiotic substrate
CYP11A	biosynthesis	cholestrol to pregnenolone	--
CYP17 (17α-hydroxylase,C_{17-20}lase)	biosynthesis	pregnenolone to 17α-hydroxypregnenolone to dehydroepiandrosterone (DHEA)	--
CYP19 (aromatase)	biosynthesis	progesterone to 17α-hydroxyprogesterone to androstenedione to estrone (E1) testosterone to estradiol (E2)	--
CYP1A1	metabolism	estrogens to 2-hydroxy estrogens	PAHs
CYP1A2	metabolism	estrogens to 2-hydroxy estrogens	heterocyclic amines
CYP1B1 (4-estrogen hydroxylase)	metabolism	estrogens to 4-hydroxy estrogens	PAHs, heterocyclic amines
CYP2C9	metabolism	estrone sulfate to 16-hydroxy sulfate	drug-paclitaxel
CYP3A3	metabolism	estrogens to 2-hydroxy estrogens	--
CYP3A4	metabolism	estrogens to 2 and 16-hydroxy	PAHs, aflatoxin
CYP3A5	metabolism	estrogensestrogens to 16α-hydroxyestrogens	Paclitaxel, vinca alkaloids, tamoxifen

PAHs-polycyclic aromatic hydrocarbons

(N.B: CYP is 'cytochrome P450 enzyme', the next numeral specifies the 'family'; the capital letter signifies the 'subfamily', and the last number designates the individual 'member').

Other discoveries about CYP 450 genes polymorphisms

CYP1B1 (P = 0.001), CYP3A5 (P = 0.001) and CYP51 (P = 0.005) presented the most noteworthy correlations with estrogen receptor status. The immune-histochemistry analysis of the expression of cytochrome P450 in breast cancer on 170 subjects with breast cancer demonstrated that, in breast cancers, CYP4X1, CYP2S1, and CYP2U1 (50.8%, 37.5%, and 32.2%, respectively) had the maximum percentage of immunopositivity. Oppositely, cyclically no immunoreactivity was observed in CYP2J and CYP3A43 (98.6% and 70.7% respectively). CYP4X1, CYP4V2, and CYP4Z1 (P = 0.01) pointed to correlations with tumor grade. Correlations with survival were documented for CYP3A4, CYP2S1, CYP4V2, and CYP26A1 (P = 0.025, 0.03, 0.026, and 0.03, respectively), yet none of these P450s was an autonomous indicator of diagnosis. This examination has revealed the expression profile of cytochrome P450s in breast cancer and could recommend their expected utilization as biomarkers to assist decisions [27].

Summary and Conclusions

The causal agent of breast cancer could not be well-defined by allelic changeability at a single locus. As an alternative, the central burden of breast cancer in the population possibly is caused by complex interactions between many genetic and environmental factors over time. An upgraded understanding of the interplay of xenobiotic contacts, endogenous physiology, and genetic variability at numerous loci might help to recognize women who are at enhanced threat for breast cancer. The genetic polymorphisms that might be associated with breast cancer are abundant. Growing lifetime contact with estrogen, estrogen metabolites, and other physiological factors, as well as environmental contacts, could show a starring role in the causal agent of breast cancer in hereditarily susceptible women. The greatest risk factors for breast cancer are associated with enhanced or extended contact with estrogen. The main influence of estrogens is thought to be via stimulation of breast-cell proliferation, thereby increasing the chances that a cell bearing a potentially cancer-causing mutation will multiply. Thus, this group of enzymes is implicated in several different biological processes including carcinogenesis, determining response to drugs, and cell signaling. In the metabolism of xenobiotic (foreign) chemicals, cytochrome P450s or monooxygenases carry out a vital function by catalyzing the hydroxylation reaction. In this review, we searched about the CYP 450 enzymes linked with the development of breast cancer which has a part the biosynthesis and metabolism of estrogens and other CYP enzymes can have a role in the emergence of breast cancer risks like CYP2C19, CYP2C8/9, CYP1A2, CYP19, CYP21, CYP17, CYP11A1, CYP2D6, CYP3A4/5, CYP1A1, CYP1B1 by reviewing other investigations. The causality of relations between genetic polymorphisms and breast cancer is unclear due to the contradiction across investigations, but the links are biologically plausible. The biological reasonableness and biological coherence of associations are less unblemished for polymorphisms that do not alter biological activity or function, and results from animal studies should also be taken into account. The temporal relationship between these inherited factors and the onset of breast cancer is clear. The strength of the associations is a significant causal criterion that may be more problematic to meet with a multifactorial disease such as breast cancer. Of specific interest are extra investigations of genes that code for those cytochrome P-450 enzymes that have a role in the

metabolism and transport of estrogen (e.g., CYP17), along with examinations of gene-environment associations and gene-gene-environment interactions (e.g., NAT2 and CYP1A1 polymorphisms and cigarette smoking in association with breast cancer threat). The molecular epidemiology investigations of breast cancer that have been conducted to date have seldom looked at a variety of potential gene-environment interactions or discovered associations and connections with more than one genetic polymorphism. Besides, few investigations have surveyed multiple endogenous factors and genetic polymorphisms in association with breast cancer risk in women, while taking causal pathways into account. The specificity of the relations is a causal standard improbable to be met since genetic polymorphisms may have an impact on the risk of a variety of ailments. Extra population-based investigations of incident cases of breast cancer, with satisfactory sample sizes and in racially diverse populations, are required to look at links with numerous genetic polymorphisms and risk factors for breast cancer (alcohol intake, diet, reproductive factors, cigarette smoking, exogenous estrogens).

References

1. Božina N, Bradamante V, Lovrić M. Genetic polymorphism of metabolic enzymes P450 (CYP) as a susceptibility factor for drug response, toxicity, and cancer risk. Archives of Industrial Hygiene and Toxicology. 2009;60(2):217-42.
2. Economopoulos KP, Sergentanis TN. Does race modify the association between CYP1B1 Val432Leu polymorphism and breast cancer risk? A critical appraisal of a recent meta-analysis. Breast cancer research and treatment. 2010;124(1):293-4.
3. Ekhart C, Doodeman VD, Rodenhuis S, Smits PH, Beijnen JH, Huitema AD. Influence of polymorphisms of drug metabolizing enzymes (CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, GSTA1, GSTP1, ALDH1A1 and ALDH3A1) on the pharmacokinetics of cyclophosphamide and 4-hydroxycyclophosphamide. Pharmacogenetics and genomics. 2008;18(6):515-23.
4. Harirchi I, Ghaemmaghami F, Karbakhsh M, Moghimi R, Mazaherie H. Patient delay in women presenting with advanced breast cancer: an Iranian study. Public Health. 2005;119(10):885-91.
5. Mousavi SM, Gouya MM, Ramazani R, Davanlou M, Hajsadeghi N, Seddighi Z. Cancer incidence and mortality in Iran. Annals of oncology. 2008;20(3):556-63.
6. Mousavi SM, Montazeri A, Mohagheghi MA, Jarrahi AM, Harirchi I, Najafi M, et al. Breast cancer in Iran: an epidemiological review. The breast journal. 2007;13(4):383-91.
7. Naghibi SA, Shojaizadeh D, Montazeri A, Yazdani Cherati J. Epidemiology of Breast Cancer in Mazandaran Province, 2009-2010. Journal of Mazandaran University of Medical Sciences. 2013;23(102):112-9.
8. Ercan B, Ayaz L, Cicek D, Tamer L. Role of CYP2C9 and CYP2C19 polymorphisms in patients with atherosclerosis. Cell Biochemistry and Function: Cellular biochemistry and its modulation by active agents or disease. 2008;26(3):309-13.
9. Fasching PA, Loehberg CR, Strissel PL, Lux MP, Bani MR, Schrauder M, et al. Single nucleotide polymorphisms of the aromatase gene (CYP19A1), HER2/neu status, and prognosis in breast cancer patients. Breast cancer research and treatment. 2008;112(1):89-98.
10. Garcia-Casado Z, Guerrero-Zotano A, Llombart-Cussac A, Calatrava A, Fernandez-Serra A, Ruiz-Simon A, et al. A polymorphism at the 3'-UTR region of the aromatase gene defines a subgroup of postmenopausal breast cancer patients with poor response to neoadjuvant letrozole. BMC cancer. 2010;10(1):36.
11. Goya M. Iranian annual cancer registration report. Ministry of health and medical education, health deputy, center for disease control and prevention. 2005.
12. Gan C, Wang X, Cao Y, Ye W, Liu H, Sun Y. Association of CYP2C19* 3 gene polymorphism with breast cancer in Chinese women. Genet Mol Res. 2011;10(4):3514-9.
13. Jiang J-G, Fu X-N, Chen C-L, Wang D-W. Expression of cytochrome P450 arachidonic acid epoxygenase 2J2 in human tumor tissues and cell lines. Ai Zheng. 2009;28(2):93-6.
14. Justenhoven C, Pierl CB, Haas S, Fischer H-P, Baisch C, Hamann U, et al. The CYP1B1_1358_GG genotype is associated with estrogen receptor-negative breast cancer. Breast cancer research and treatment. 2008;111(1):171-7.
15. Khedhaier A, Hassen E, Bouaouina N, Gabbouj S, Ahmed SB, Chouchane L. Implication of xenobiotic metabolizing enzyme gene (CYP2E1, CYP2C19, CYP2D6, mEH and NAT2) polymorphisms in breast carcinoma. BMC cancer. 2008;8(1):109.
16. Mariotto AB, Robin Yabroff K, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010–2020. Journal of the National Cancer Institute. 2011;103(2):117-28.
17. Murray GI, Patimalla S, Stewart KN, Miller ID, Heys SD. Profiling the expression of cytochrome P450 in breast cancer. Histopathology. 2010;57(2):202-11.
18. Rodgers KM, Udesky JO, Rudel RA, Brody JG. Environmental chemicals and breast cancer: an updated review of epidemiological literature informed by biological mechanisms. Environmental research. 2018;160:152-82.
19. Salimi S, Sajadian M, Khodamian M, Yazdi A, Rezaee S, Mohammadpour-Gharehbagh A, et al. Combination effect of cytochrome P450 1A1 gene polymorphisms on uterine leiomyoma: A case-control study. Bosnian journal of basic medical sciences. 2016;16(3):209.
20. Sim SC, Ingelman-Sundberg M. Update on allele nomenclature for human cytochromes P450 and the Human Cytochrome P450 Allele (CYP-allele) Nomenclature Database. Cytochrome P450 Protocols: Springer; 2013. p. 251-9.
21. Sissung TM, Danesi R, Price DK, Steinberg SM, De Wit R, Zahid M, et al. Association of the CYP1B1* 3 allele with survival in patients with prostate cancer receiving docetaxel. Molecular cancer therapeutics. 2008;7(1):19-26.
22. Stingl JC, Parmar S, Huber-Wechselberger A, Kainz A, Renner W, Seeringer A, et al. Impact of CYP2D6* 4 genotype on progression free survival in tamoxifen breast cancer treatment. Current medical research and opinion. 2010;26(11):2535-42.
23. Zhou S-F. Drugs behave as substrates, inhibitors and inducers of human cytochrome P450 3A4. Current drug metabolism. 2008;9(4):310-22.
24. Zhou M, Maitra SR, Wang P. The potential role of transcription factor aryl hydrocarbon receptor in downregulation of hepatic cytochrome P-450 during sepsis. International journal of molecular medicine. 2008;21(4):423-8.
25. Wegman P, Elingarami S, Carstensen J, Stål O, Nordenskjöld B, Wingren S. Genetic variants of CYP3A5, CYP2D6, SULT1A1, UGT2B15 and tamoxifen response in postmenopausal patients with breast cancer. Breast Cancer Research. 2007;9(1):R7.
26. Wu Y, Qu X, Xia J, Gu Y, Qian Q, Hong Y. Four CYP19A1 Polymorphisms and Breast Cancer Risk: A MetaAnalysis. Journal of Biochemistry and Physiology. 2018;2018.
27. Ruiter R, Bijl MJ, Van Schaik RH, Berns EM, Hofman A, Coebergh J-WW, et al. CYP2C19* 2 polymorphism is associated with increased survival in breast cancer patients using tamoxifen. Pharmacogenomics. 2010;11(10):1367-75.