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Review

The effect of genetic variability on drug response in conventional breast cancer treatment

Emilia Wiechec, Lise Lotte Hansen *

Institute of Human Genetics, The Bartholin Building, University of Aarhus, DK-8000 Aarhus C, Denmark

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ABSTRACT

The conventional breast cancer diagnosis based mainly upon histopathology, hormone and HER-2 receptor status, will in the future be combined with information on genomic and epigenetic profiles of the individual patient. This will lead to an optimal personalized therapy, directed towards specific genomic aberrations, avoiding unnecessary toxicity, side effects and chemotherapeutic drugs for which the patient evolves resistance. Breast cancer is a very heterogeneous malignancy, expressing a considerable variation in genomic aberrations from deletions and amplifications comprising entire chromosomes to minor regions. A wide spectrum of differently expressed genes and mutations has been identified, adding information to the highly complex picture of the tumor genome. The vast majority of breast cancer incidents is of somatic origin and may be caused by a combination of the individual genetic profile and environmental exposure. A major contributor to the variation in genetic profile is the single nucleotide polymorphisms (SNPs), which are highly abundant throughout the genome, and both current and future methodologies have the potential to screen millions of SNP genotypes in one analysis. Identification of specific SNP genotypes affecting transcriptional activity and thereby the outcome for the patient, of genes involved in DNA repair, metabolizing of chemotherapeutic drugs and drug target genes will determine the outcome for the patient. This will be an essential part of the development of personalized treatment of cancer. In this review the focus is on clinically relevant SNPs in genes implicated in drug metabolism and disposition as well as their influence on breast cancer therapy toxicity and/or efficacy.

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* Corresponding author. Tel.: +45 8942 1680, +45 2899 2180 (Cell phone); fax: +45 8612 3173.
E-mail address: lotte@humgen.au.dk (L.L. Hansen).

1. Introduction

Breast cancer is the most common malignancy in women presenting a lifetime risk of 8%. Breast cancer mortality has declined briefly over the past years but is still the leading cause of cancer death for women (Boyle and Ferlay, 2005a,b; Cardis et al., 2006; Ferlay et al., 2007).

Breast cancer is a multifactorial disease, and less than 10% of all incidents are considered caused by defects in single genes (monogenic). For the majority of incidents, the multiple steps leading to breast tumorigenesis are not fully elucidated despite a comprehensive effort worldwide. New breast cancer susceptibility genes have been identified, though less penetrant as the well characterized BRCA1 and BRCA2. Epigenetic studies, especially targeting changes in the methylation pattern of tumor DNA are promising new markers for risk, early diagnosis and therapy prediction. Genomic aberrations as single nucleotide polymorphisms (SNPs) and copy number variations are used in association studies comparing genotype frequencies and copy number variations between affected and non-affected individuals to assess new cancer susceptibility genes and markers predicting therapy response and drug resistance. Mapping of the variety of epigenetic and genomic alterations in tumor genomes and correlating these finding with tumor characteristics, prognosis and response to therapy are the first steps towards generating personalized therapy.

The choice of breast cancer therapy is based on tumor characteristics such as size, histopathology, estrogen and progesterone receptor status, the level of HER-2 expression, and lymph node infiltration. Therapy includes surgery (lumpectomy, mastectomy), radiotherapy, hormonal therapy, chemotherapy, and immunotherapy. Neoadjuvant radiotherapy can be used in combination with an early diagnosis in order to diminish the size of the tumor prior to surgery.

Breast tumors with high expression of estrogen and progesterone receptors are treated with estrogen receptor inhibitors as tamoxifen. Recently, a new group of estrogen synthesis inhibitors, the aromatase inhibitors have been implemented in treatment of postmenopausal breast cancer (Brueggemeier, 2004; Gibson et al., 2007). This group of anticancer drugs seems to be more attractive in comparison to tamoxifen, mostly due to lower toxicity. Furthermore, a list of cytotoxic drugs applied either separately or in combination chemotherapy comprises an efficient strategy for treatment of advanced or metastatic breast cancer. However, the outcome of anticancer therapy varies greatly from patient to patient, and it is becoming clear that the individual genetic profile plays a dominant role. Loss of the efficacy of the treatment followed by the severe toxicity as: myelosuppression, secondary leukemia, moist desquamation of the skin, nausea, fatigue, and diarrhea are common events in ineffective response to pharmacotherapeutics.

Most interpatient differences in the therapy efficacy and/or toxicity lies in the genetic variability described by SNPs and copy number variations, which affect the anticancer drug metabolism pathways and target genes of the chemotherapeutics used in cancer therapy. The comprehensive impact of heritable polymorphisms on drug response and therapy-induced toxicity has been studied intensively in the past decades, rapidly increasing after the release of the first draft of the human genome sequence, and is known as pharmacogenetics (Gibson et al., 2007; Nebert, 1982; Sjoqvist, 1999). The importance of genetic variations in prediction of the anticancer drug activity prompts the development of personalized medicine where the choice of treatment is based on the individual's genetic profile. This individualized genotype map results in various phenowell as the efficacy of treatment. The pharmacokinetics of an administered drug can be altered by genetic variations on the level of genes involved in drug uptake, activation, distribution, anticipated action, and excretion (Fig. 1).

In this review we emphasize the predictive role of SNPs in cancer treatment. As examples we describe the genetic variants in the genes responsible for transport of cytotoxic agents, metabolism and drug-associated target genes with focus on their impact on breast cancer therapy toxicity/efficacy. The key genes implicated in the metabolism of anticancer drugs and therapy responsive genes as well as the predicted effect of genetic polymorphisms within these genes in anticancer therapy are listed in Tables 1 and 2 respectively.

2. SNP analysis

A single nucleotide polymorphism (SNP) is defined as a variation of one nucleotide in which one allele is present in more than 1% of the studied population. SNPs are biallelic though tri- or tetraallelic forms have been found (Huebner et al., 2007). Non-biallelic SNPs are rare and can be overlooked as many frequently used genotyping methodologies fail to detect the additional alleles (Huebner et al., 2007).

It is estimated that the genome contains approximately 10 million SNPs of which 3.1 million are validated via the HapMap project (2003; Frazer et al., 2007). In the second phase of the HapMap project 270 individuals from four geographical diverse populations were genotyped for 2.1 million SNPs, which means that 25–30% of all genomic SNPs with a minor allele frequency ≥ 0.05 are validated (Frazer et al., 2007). The SNP density is in average one genotyped SNP per 875 bp (or 1.14 SNP/1000 bp) though not distributed evenly through out the genome. The SNP frequency is lower in genomic regions, conserved betweeen spieces including coding regions than in non-coding parts of the genome (Li and Sadler, 1991; Nickerson et al., 1998).

SNPs in non-coding genomic regions, which are less conserved among spieces, are generally frequent and highly plymorphic, making them usefull for population based studies of evolution or as physical or genetic markers in genome-wide search for new disease susceptibility genes. In selected patient cohorts undergoing cancer therapy, these SNP

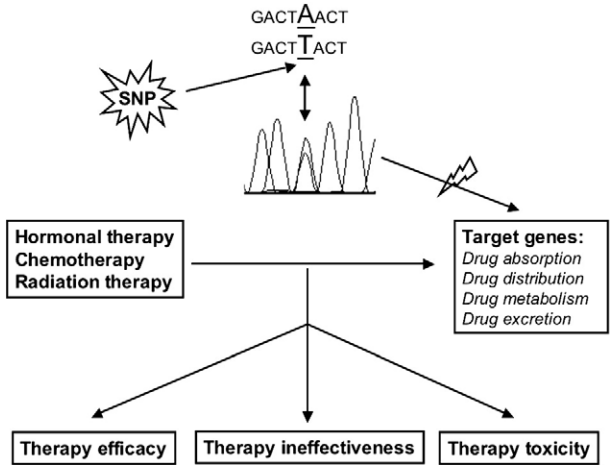

Fig. 1. Influence of SNPs on toxicity/efficacy of breast cancer therapy. Interpatient variability plays a crucial role in selecting the accurate treatment option as well as predicting its clinical

Table 1
List of candidate genes with impact on the anticancer drug metabolism, drug interactions and therapy efficacy.

Gene	Name	Cytogenetic location	Function of the gene product
MDR1	Multidrug resistance 1	7q21.1	Drug transporter; implicated in energy-dependent transport of cytotoxic agents out of the cell
SLC22A16	Solute carrier family 22, member 16	6q21–22.1	Organic cation transporter involved in transport of various compounds including hormones, neurotransmitters and xenobiotics (doxorubicin)
CYP1B1	Cytochrome P450, family 1, subfamily B, polypeptide 1	2p21	Phase I enzyme in drug metabolism; metabolism of estrogens in human breast tissue; synthesis of cholesterol and lipids
CYP2B6	Cytochrome P450, family 2, subfamily B, polypeptide 6	19q13.2	Phase I enzyme in metabolism of anticancer drugs cyclophosphamide; synthesis of cholesterol and lipids
CYP2D6	Cytochrome P450, family 2, subfamily D, polypeptide 6	22q13.1	Phase I enzyme involved in metabolism of antiestrogens such as tamoxifen
CYP19A1	Cytochrome P450, family 19, subfamily A, polypeptide 1; Aromatase	15q21.1	Phase I enzyme in drug metabolism; biosynthesis of estrogens
SULT1A1	Sulfotransferase family 1A, member 1	16p12.1	Phase II enzyme in drug metabolism; catalyzes the sulfate conjugation of drugs, hormones and xenobiotics as a detoxication mechanism for phenolic and estrogenic compounds (4-hydroxy-tamoxifen)
GSTP1	Glutathione S-transferase pi 1	11q13.2	Phase II enzyme in drug metabolism; catalyzes the conjugation of a reduced glutathione to smooth the excretion of xenobiotics from the body
NQO1	NAD(P)H: quinone oxidoreductase 1	16q22.1	Phase II enzyme in drug metabolism; reduces quinone-based anticancer agents to hydroquinones protecting against oxidative stress, production of reactive-oxygen species and carcinogenesis
CES2	Carboxylesterase 2	16q22.1	Phase II enzyme required for the transformation of the pro-drug, capecitabine into 5-Fluorouracil
MTHFR	5,10-Methylenetetrahydrofolate reductase	1p36.3	Enzyme responsible for metabolism of vitamin B9 (folate) required in DNA synthesis
TS	Thymidylate synthase	18p11.32	Enzyme implicated in conversion of deoxy-uridine monophosphate (dUMP) into deoxy-thymidine monophosphate (dTMP) which is essential in DNA synthesis
DPD	Dihydropirymidine dehydrogenase	1p22	Enzyme involved in degradation of pyrimidines (uracil and thymine) and uracil analogue used in chemotherapy, 5-Fluorouracil
CDA	Cytidine deaminase	1p36.2–p35	Enzyme involved in the retrieval of pyrimidines and detoxifying the anticancer drug, gemcitabine
XRCC1	X-ray repair complementing defective repair in Chinese hamster cells 1	19q13.2	The base excision repair (BER) protein capable to restore DNA single-strand breaks emerged due to exposure to ionizing radiation and alkylating agents
APE1	Apurinic/apyrymidinic endonuclease 1	14q11.2–q12	Enzyme involved in the repair of DNA abasic sites generated spontaneously or by radiation-derived genotoxic agents
SOD2	Superoxide dismutase 2	6q25.3	Enzyme from the primary antioxidant defense group catalyzing conversion of superoxide (O_2^-) into hydrogen peroxide (H_2O_2) and oxygen
MPO	Myeloperoxidase	17q23.1	Enzyme from the host defense system group producing hypochlorous acid (HOCl) from hydrogen peroxide which possess strong antimicrobial activity
RRM1	Ribonucleotide reductase M1	11p15.5	Enzyme involved in production of deoxyribonucleotides necessary for DNA synthesis and repair
TGFβ1	Transforming growth factor beta 1	19q13.1	Cytokine controlling cell growth, proliferation, differentiation and apoptosis
FGFR4	Fibroblast growth factor receptor 4	5q35.1	Protein involved in a number of cellular processes such as cell growth, differentiation, migration, angiogenesis
ATM	Ataxia telangiectasia mutated	11q22–q23	Protein involved in regulation of DNA damage response and cell cycle control
TP53	Tumor protein 53	17p13.1	Protein involved in a variety of cellular mechanisms such as: apoptosis, cell cycle, DNA repair; important tumor suppressor in many types of cancer

association studies can lead to identification of SNP genotypes involved in therapy response and resistance.

Non-synonomous SNPs may affect the amino acid composition of a protein, either as missense or non-sense mutations. Most protein coding regions are highly conseved among spieces and therefore, non-synomous SNPs are characterized by a low frequency and a minor allele frequency. Likewise, SNPs in regulatory regions as promoters, 5′ or 3′ UTRs, microRNAs, enhancer or silencer elements may affect the transcriptional activity of genes and therefore, are rare SNPs with minor allele frequency.

The vast majority of SNPs reported to public databases are highly polymorphic SNPs, but it is estimated that more than 60% of all SNPs in the human genome have a minor allele frequency <5% (Gorlov et al., 2008; Wong et al., 2003). Low minor allele frequency SNPs include SNPs in coding and regulatory regions and in combination with the new high throughput genotype detecting methodologies, which provide the possibility to screen large populations for a high number of SNPs, these SNPs have a strong potential as disease risk markers (Zhu et al., 2004). Rare low minor allele frequency SNPs are included in genotyping platforms, which will facilitate the identification of causal large (Gorlov et al., 2008). SNP genotypes either alone or in combination as haplotypes are important tools in the search for the origin of multifactorial diseases in which multiple affected genes and enviromental factors can be combined to the set of the disease. Haplotypes can be established by SNP genotypes along the chromosomes in sperm cells, via family studies or in large populations. Haplotypes are inherited in blocks (haplotype blocks), which rarely are interferred by recombination. Haplotype blocks, therefore, represent genotypes in linkage disequilibrium and are important in the search for disease susceptibility genes or genes affecting drug response. SNP genotypes in genomic regions between haplotype blocks are not in linkage disequilibrium and may represent recombination hot spots (Jeffreys et al., 2005). Data from phase II of the HapMap project identified 32,996 recombination hotspots in the human nuclear genome. No marked difference was found between chromosomes in the concentration of recombination hotspots (Frazer et al., 2007).

The rapidly increasing amount of validated SNPs across the genome is a valuable tool to identify new disease susceptibility genes for multifactorial diseases. Association studies comparing SNP genotypes be-

Table 2
Genetic polymorphisms influencing the drug response and toxicity in breast cancer treatment.

Drug	Drug target gene	Variant allele	Effect of the polymorphism on the efficacy/toxicity of drug therapy and clinical outcome
Adjuvant hormonal therapy			
Tamoxifen	CYP2D6	CYP2D6*4/*4	Higher risk of disease recurrence (Goetz et al., 2005)
		CYP2D6*10/*10	Higher risk of disease recurrence (Kiyotani et al., 2008)
		CYP2D6*4	Lower risk of disease recurrence, severe hot flashes (Wegman et al., 2005)
	SULT1A1	SULT1A1*2/*2 (homozygous variant)	Increased risk of death (Nowell et al., 2002)
Aromatase inhibitors (letrozole, anastrazole)	CYP19A1	Rs4646 (GT or TT)	High response to letrozole, improved treatment efficacy (Colomer et al., 2008)
Chemotherapy			
Cyclophosphamide	GSTP1	GSTP1-01 (GG or AG) — Rs1695	Increased risk of disease progression and death (Bewick et al., 2008)
	SOD2	SOD2-01(TT) — Rs4880	Chemotherapy induced increased risk of disease progression and death (Bewick et al., 2008)
		SOD2-01(CC) — Rs4880	Improved survival outcome (Bewick et al., 2008)
	MPO	MPO-02(GG) — Rs2333227 + SOD2-01(CC)	Decreased risk of death (Ambrosone et al., 2005)
	CYP2B6	CYP2B6*1A/*1A	Severe leucocytopenia (Nakajima et al., 2007)
Methotrexate	MTHFR	Rs1801133: C677T (TA)	Decreased chemosensitivity of breast cancer cells (Sohn et al., 2004)
		Rs1801133: 677(TT/CT) + Rs1801131: 1298(AA)	Increased risk of developing secondary leukemia (Guillem et al., 2007)
5-Fluorouracil	MTHFR	Rs1801133: C677T (TA)	Increased chemosensitivity to 5-Fluorouracil (Sohn et al., 2004)
	DPD	IVS14 + 1G>A (rs3918290)	Neurotoxicity and death, myelosuppression (Raida et al., 2001; Takimoto et al., 1996; van Kuilenburg, 2004; van Kuilenburg et al., 2001)
Capecitabine	CES2	6046 G>A	Higher incidence of grade 3 hand–foot syndrome and grade 3–4 diarrhea (Ribelles et al., 2008)
		−823 C>G	Better response to capecitabine and longer time to progression of the malignancy (Ribelles et al., 2008)
Gemcitabine	TP53	72Pro>Pro (rs1042522)	Poor disease-free survival, decreased sensitivity to neoadjuvant chemotherapy (Toyama et al., 2007; Xu et al., 2005)
	RRM1	2455 A>G	Low frequency of neutropenia, poor overall survival, indicator of resistance to gemcitabine (Rha et al., 2007)
		2464 G>A	
	CDA	208 G>A	Significant decrease in gemcitabine clearance; increased risk for neutropenia with co-administration of 5-Fluorouracil, cisplatin or carboplatin (Sugiyama et al., 2007)
Mitomycin	TS	5′ UTR: 28 bp 3× tandem repeat	Treatment-specific reduced survival (Nordgard et al., 2008)
Doxorubicin	MDR-1	3435 (TT)	Complete clinical response to neoadjuvant doxorubicin-based chemotherapy (Kafka et al., 2003)
		1236 (CC) + 2677 (GG) + 3435 (CC)	Increased clearance of doxorubicin (Lal et al., 2008)
	SLC22A16	146 (GG)	Higher exposure level to doxorubicinol (Lal et al., 2007)
Epirubicin	NQO1	NQO1*2(SS)	Poor survival rate in epirubicin treated breast cancer patients; impairment of response to epirubicin; strong prognostic and predictive factor in breast cancer (Fagerholm et al., 2008)
Paclitaxel	CYP1B1	CYP1B1*3 (homozygous variant)	Longer progression-free survival in breast cancer patients; paclitaxel resistance (Gehrmann et al., 2008; Marsh et al., 2007)
Combination chemotherapy			
CMF	XRCC1	1196(AA)	Reduced risk for recurrence/death (Jaremko et al., 2007)
	FGFR4	Arg388	Poor disease-free survival and overall survival for node-positive breast cancer patients; poor therapy response (Thussbas et al., 2006)
Neoadjuvant radiation/FAC/CMF	TGFβ1	TGFβ1 (Pro/Pro)	Greater radiation toxicity; better pathologic complete response to FAC (Rajkumar et al., 2008)
Radiotherapy			
	TGFβ1	−509 C>T	Increased radiosensitivity of normal breast tissue and subsequent radiation-induced tissue complications (Andreassen et al., 2005, 2003)
		10 Leu/Pro	
	ATM	5557 G>A	Lower risk for development of radiation-induced subcutaneous fibrosis (Andreassen et al., 2006a,b)
	XRCC1	399 Arg/Arg	Increased risk of radiation-induced subcutaneous fibrosis (Andreassen et al., 2006a)
	XRCC1	$XRCC1^{399}Gln$	Lower risk of acute moist desquamation of the skin (Chang-Claude et al., 2005)
	APE1	$APE1^{148}Glu$	

CMF (cyclophosphamide, methotrexate, 5-Fluorouracil) and FAC (cyclophosphamide, doxorubicin, 5-Fluorouracil).

of unaffected individuals, may identify causative SNP genotypes or SNP genotypes increasing the risk of disease.

The identification of a causative SNP or a gene is the first step towards development of personalized medicine. The SNP genotype may be decisive for the optimal treatment for each individual patient taking into accout the risk of resistance towards specific chemotherapeutic agents, change in the activity of the gene product or developing severe side effects. The SNPs positioned in the key genes involved in the drug metabolic pathway and genes associated with drug treatment in breast

3. Drug metabolism

The biotransformation of xenobiotics from their lipophilic structure into water-soluble and excretal form involves a number of metabolizing enzymes and is carried out mainly in the liver. Moreover, drug absorption, delivery and their secretion across biological membranes profoundly affect their pharmacokinetics, and are affected by drug transporters. The two major phases, phases I and II in drug metabolism lead to complete modification and inactivation of an administered drug

et al., 2005; Liska, 1998). The initial phase I is implicated in drug activation/inactivation and preparation for phase II transformation characterized by oxidation, reduction and hydrolysis reactions. Phase II transformation of drugs involves conjugation of a drug or its initially transformed phase I metabolite with an endogenous substrates in the liver as a result of acetylation, amino acid conjugation, glucuronidation, sulfate conjugation and glutathione conjugation. The kidneys can successfully excrete these phase II hydrophilic conjugates. The efficiency of all the mentioned steps in drug metabolism as well as the host response to the drug treatment is highly dependent on the genetic polymorphisms in the drug metabolizing enzymes, patients' age and the health-status of drug detoxifying organs (George et al., 1990; Nolin et al., 2008; O'Mahony and Woodhouse, 1994; Prescott et al., 1975; Woodhouse and Wynne, 1988). Any failure in this machinery caused by these factors, with a special distinction of SNP genotypes present in the drug-responsive genes might lead to therapy toxicity or drug resistance.

4. Drug transporters

The ABC transporters (*A*TP-*B*inding *C*assette transporters) comprise a family of transmembrane proteins which use ATP hydrolysis as a power source for transport activity (Dean et al., 2001; Higgins, 1992). They have recently attracted a lot of attention due to their high expression in (cancer) stem cells (Hombach-Klonisch et al., 2008; Klonisch et al., 2008) Seven major subfamilies of the ABC transporters genes exist, however, only three of them (ABCB, ABCC, ABCG) are involved in drug transport including anticancer drugs (Gillet et al., 2004; Gottesman et al., 2002). Genetic polymorphisms affecting these transporters contribute to interpatient differences in drug response. One of the 49 members of ABC transporters, the P-glycoprotein encoded by the multidrug resistance gene MDR1 (ABCB1) plays an important role in efflux transport of the chemotherapeutic agent, doxorubicin used in breast cancer treatment (Klein et al., 1999). A substantial number of SNPs in the MDR1 gene, their influence on the gene function and response to drug therapy has been reported (Dey, 2006; Fromm, 2002; Kim, 2002; Sai et al., 2003; Saito et al., 2002). However, little is known about importance of genetic variations in MDR1 to the breast cancer chemotherapy. A synonymous SNP consisted of C-to-T transition at nucleotide 3435 in exon 26 has shown a considerable advantage in neoadjuvant chemotherapy. The 3435 TT genotype was associated with complete response to chemotherapy in patients treated with doxorubicin (Kafka et al., 2003). In another study, the clearance of this drug was significantly improved in breast cancer patients possessing the combined 1236 CC + 2677 GG + 3435 CC genotype (Lal et al., 2008).

The other class of transporters, which play a critical role in drug absorption and elimination, are organic cation transporters (OCT). As the name suggests, they utilize the ion gradient across the membrane in order to facilitate transport of substrates against the electrochemical difference (Koepsell et al., 2007, 2003; Okabe et al., 2005). The influx cation transporter — SLC22A16 was evaluated in Asian breast cancer patients in regard to response to treatment with doxorubicin. The 146 GG genotype was linked to higher exposure level to doxorubicin (Lal et al., 2007).

5. Drug metabolizing phase I enzymes

5.1. Cytochrome P450

Cytochromes P450 (CYP) comprise a comprehensive family of isoenzymes involved in drug metabolism as phase I enzymes, ubiquitously expressed in the liver and intestine. They catalyze the monooxygenase reaction in order to inactivate (or activate) drugs and toxic compounds. Among human cytochromes P450 four families stand out, CYP1, CYP2, CYP3 and CYP19, which are involved in metabolism of anticancer drugs, as tamoxifen, aromatase inhibitors, cyclophosphamide number of genetic polymorphisms in the CYP genes has been linked to the outcome of the drug therapy in breast cancer patients (Ingle, 2008).

The metabolic pathway of the two major, estrogen receptor-positive breast cancer drugs, tamoxifen and aromatase inhibitors are influenced by cytochrome P450 enzymes. The member of CYP2 family, CYP2D6 enzyme, transforms antiestrogenic tamoxifen into its secondary metabolite, 4-hydroxy-N-desmethyl-tamoxifen known as endoxifen (Stearns et al., 2003; Stearns and Rae, 2008). Functional SNPs within this gene are reported to be implicated in the long-term outcome of the tamoxifen-based therapy. Breast cancer patients carrying the CYP2D6*4/*4 or CYP2D6*10/*10 alleles have much higher risk of disease recurrence in comparison to having the CYP2D6*4 allele (Goetz et al., 2005; Kiyotani et al., 2008; Wegman et al., 2005).

Aromatase inhibitors block the cytochrome CYP19 (aromatase) synthesizing endogenous estrogen from androgens (Brueggemeier, 2004). Therefore, they have considerable impact on current adjuvant treatment of breast cancer (Smith, 2003; Smith and Dowsett, 2003). The CYP19A1 rs4646 SNP is linked to higher efficacy of the treatment as well as higher response to aromatase inhibitors (Colomer et al., 2008).

Alkylating agents, as cyclophosphamides are one of the chemotherapeutic drugs applied to treat breast cancer. It requires metabolic activation to the primary metabolite, 4-hydroxycyclophosphamide (4-OH-CPA) by various cytochrome P450 enzymes including CYP2B6 (Chang et al., 1993; Code et al., 1997). One of the allelic variant, CYP2B6*1A/1A was found to correlate with development of severe leucocytopenia in cancer patients (Nakajima et al., 2007).

A further example of anticancer drugs metabolized by cytochromes P450 including CYP2C8, CYP3A4 and CYP3A5 is the microtubule target, paclitaxel (Steed and Sawyer, 2007). However, little is known about genetic polymorphisms in CYPs and paclitaxel toxicity in breast cancer. Surprisingly, recent studies have shown that the CYP1B1*3 polymorphism in the breast tissue-associated CYP1B1 gene is linked with longer progression-free survival and paclitaxel resistance in breast cancer (Gehrmann et al., 2008; Marsh et al., 2007).

6. Drug metabolizing phase II enzymes

6.1. Sulfotransferases

The enzyme Sulfotransferase 1A1 (SULT1A1) catalyzes the sulfation reaction of various phenolic and estrogenic substrates including transformation of 4-hydroxy-tamoxifen (Falany et al., 1994). Analysis of genetic variants has shown that patients treated with tamoxifen, who are homozygous for the SULT1A1*2 allele, had three fold higher risk of death when compared with patients carrying the SULT1A1*1allele (Nowell et al., 2002).

6.2. Glutathione S-transferase pi

Glutathione S-transferase pi 1 (GSTP1) is an important enzyme in conjugation of hydrophobic compounds with a reduced glutathione, thus increasing their-water solubility and often facilitating excretion (Coles and Kadlubar, 2003). Metabolites of widely used chemotherapeutics in treatment of breast cancer, cyclophosphamides and doxorubicin comprise the substrates for GSTP1 activity (Stearns et al., 2004). The rs1695 (GG or AG) genotype was found to correlate significantly with unfavorable prognosis for breast cancer patients treated with alkylating agents (Bewick et al., 2008).

6.3. NAD(P)H: quinone oxidoreductase 1

NAD(P)H: quinone oxidoreductase 1 (NQO1) catalyzes reduction of quinines, quinone amines and nitro substrates utilizing NADP or NADPH as reducing cofactors (Edwards et al., 1980; Ross et al., 2000;

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