Polymorphisms of phase I and phase II enzymes and breast cancer risk

Christina Justenhoven1,2*

1 Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany
2 University of Tübingen, Tübingen, Germany

INTRODUCTION

The implementation of cost effective high-throughput genotyping methods enables the determination of genotypes at large scale and fast pace. These improvements are prerequisite of the in depth investigation of the polygenetic basis of complex diseases. Prominent examples are genome-wide association studies which led to the identification of novel breast cancer risk factors such as polymorphisms in FGFR2, CCND1, TOX3, MAP3K1, LSP1, CDKN2A, and 2B (Easton et al., 2007; Lambrechts et al., 2012). However, a shortcoming of this comprehensive approach is the exclusion of the majority of genes encoding phase I and II enzymes, because their special genomic architecture hampers the assessment of accurate genotype data. It is necessary to overcome this limitation due to the fact that functional genetic variations in these genes are known to alter expression, activity, and stability of the encoded enzymes causing defective inactivation and excretion of hormones as well as environmental toxicants (Thompson and Ambrosone, 2000; Reszka et al., 2006). Thus, it is of high relevance to understand the potential impact of these polymorphisms in pathogenic processes such as carcinogenesis. In addition, these phase I and II enzymes play a pivotal role in activation and metabolism of drugs with the potential to trigger therapy response as well as occurrence of adverse side effects (Meyer et al., 2012). With respect to breast cancer pharmacogenetic investigations revealed the impact of a genetical determined poor metabolizer phenotype of the phase I enzyme cytochrome P450 (CYP) 2D6 and tamoxifen treatment outcome (Schröth et al., 2009). This finding has been a matter of debate due to reports on conflicting results that seem to be based on inaccurate genotype data (Brauch et al., 2012). Amongst others this finding underlines the need of specific genotyping methodologies for genes encoding metabolic enzymes. This review will focus on studies investigating the role of genetic variants of phase I and II enzymes in breast cancer risk that used validated genotyping methods.

BREAST CANCER RISK

Breast cancer is a multifactorial disease and it is known that the carcinogenic process is affected by several endogenous as well as exogenous factors (Rebbeck et al., 1997). In this respect, steroid hormones play a pivotal role (Key et al., 2002b). Epidemiological studies indicated an increased breast cancer risk in women with prolonged exposure to sex hormones, e.g., early menarche and late menopause (Henderson and Feigelson, 2000; Clemons and Goss, 2001). Moreover, observational studies revealed the risk effect of exogenous hormones such as postmenopausal hormone replacement therapy (HR); Rossouw et al., 2002; Beral and Million Women Study Collaborators, 2003; Pesch et al., 2005; Flesch-Janys et al., 2008) and oral contraceptives (Collaborative Group on Hormonal Factors in Breast Cancer, 1996; Kahlenborn et al., 2006). The strong correlation between circulation steroid hormones and breast cancer risk is supported by an observation of a two-fold increased risk for women with elevated sex hormone levels (Key et al., 2002a; Eliassen et al., 2006). A functional explanation of these findings comes from in vitro and in vivo studies that indicated initiation, promotion, and progression of breast tumorigenesis by estrogens and their metabolites (Nandi et al., 1995; Yue et al., 2003; Turan et al., 2004). This effect has been attributed to estrogen-induced gene expression of factors involved in cell growth and division (Liu and Lin, 2004) as well as genotoxic action of metabolic compounds such as 4-hydroxy catechol estrogens and estrogen-3,4-quinones (Yager and Davidson, 2006). Moreover, progesterone adds to hormone-induced carcinogenesis by promotion of estrogen synthesis, estrogen receptor expression, and cell proliferation (Poutanen et al., 1995; Shyamala et al., 2002;
As of today less than 5% of familial breast cancer were attributed to ATM (UGTs), inactive and water soluble compounds which can be easily excreted to a more polar molecule, a process that usually produces (Guengerich, 1999). In most cases phase I metabolism is followed by phase II metabolism where the major mediators of this phase are cytochrome P450 (CYP) enzymes or hydroxylation yielding more polar metabolites; the predominant substrates usually undergo reduction, oxidation, conjugation and transporters have been developed within recent years: the CYP2C19, CYP2D6, CYP2C9, CYP3A and GST enzymes, as well as NATs and UGTs (Salinas and Wong, 1999; Gellner et al., 2001; Tukey and Strassburg, 2001; Nelson et al., 2004; Sim et al., 2008). So far individual assays for some of these polymorphisms have been established by researchers, e.g., for CYP3A (Justenhoven et al., 2010; The MARIE-GENICA Consortium on Genetic Susceptibility for Menopausal Hormone Therapy Related Breast Cancer Risk, 2010), CYP2D6 (Schaeffeler et al., 2003; Morike et al., 2008), CYP2C19 (Justenhoven et al., 2012), GST, UGT, and SULT1A (The MARIE-GENICA Consortium on Genetic Susceptibility for Menopausal Hormone Therapy Related Breast Cancer Risk, 2010) as well as companies (e.g., Applied Biosystems and Third Wave Technologies) 1,2. Moreover, particular panels and arrays for the genetic analysis of metabolic enzymes and transporters have been developed within recent years: the AmpliChip® CYP P450 Test 3, the DMET Plus Panel DNA Chip4, VeraCode ADME Core Panel5, and the iPLEX ADME PGx Panel6. These tools were initially launched to support pharmacogenomic testing in clinical research and diagnostics, however, their coverage of relevant genes is still incomplete but they provide a convenient basis for a variety of investigations dealing with diverse health issues.

1http://www.appliedbiosystems.com
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CHALLENGES OF GENOTYPING
The majority of phase I and II enzymes are encoded by related genes which constitute gene families and subfamilies depending on their degree of sequence similarities. This particular genomic architecture hampers specific genotyping due to the potential co-amplification of homolog gene sequences. Therefore, the establishment of accurate analysis methods requires primer selection by eye inspection, adapted amplification protocols, and verification of genotype calls by an independent method (Justenhoven et al., 2010). An example for the particular need of an appropriate genotyping procedure is the analysis of the SULTA1 638 G > A (rs9282861) polymorphism. The human SULTA1 subfamily comprises three genes SULTA1A, SULTA1B, and SULTA1C which are located in close proximity on the short arm of chromosome 16 and share sequence similarities of more than 90% (Hempel et al., 2005). Due to these remarkable homologies the selection of applicable primers which enable specific amplification of the SULTA1 638 G > A region is difficult (Figure 1). Usually automatic assay design tools generate inappropriate primers for such sequences which lead to simultaneous amplification of all members of a gene subfamily resulting in incorrect genotype calls due to abundance of the relevant allele (Figure 2A). Valid assays include the identification of primer binding sites in unique DNA regions of the respective gene and adapted annealing temperatures, only such highly selective amplification conditions assure correct genotype calls (Figure 2B). Other gene families and subfamilies with a similar degree of sequence homologies are known for CYP3A, CYP2C, GSTs, as well as NATs and UGTs (Salinas and Wong, 1999; Gellner et al., 2001; Tukey and Strassburg, 2001; Nelson et al., 2004; Sim et al., 2008). So far individual assays for some of these polymorphisms have been established by researchers, e.g., for CYP3A (Justenhoven et al., 2010; The MARIE-GENICA Consortium on Genetic Susceptibility for Menopausal Hormone Therapy Related Breast Cancer Risk, 2010), CYP2D6 (Schaeffeler et al., 2003; Morike et al., 2008), CYP2C19 (Justenhoven et al., 2012), GST, UGT, and SULT1A (The MARIE-GENICA Consortium on Genetic Susceptibility for Menopausal Hormone Therapy Related Breast Cancer Risk, 2010) as well as companies (e.g., Applied Biosystems and Third Wave Technologies) 1,2. Moreover, particular panels and arrays for the genetic analysis of metabolic enzymes and transporters have been developed within recent years: the AmpliChip® CYP P450 Test 3, the DMET Plus Panel DNA Chip4, VeraCode ADME Core Panel5, and the iPLEX ADME PGx Panel6. These tools were initially launched to support pharmacogenomic testing in clinical research and diagnostics, however, their coverage of relevant genes is still incomplete but they provide a convenient basis for a variety of investigations dealing with diverse health issues.

THE ROLE OF PHASE I AND II ENZYMES IN CARCINOGENESIS
Phase I and II enzymes are of particular interest with respect to breast cancer due to their involvement in the metabolism of steroid hormones, chemical carcinogens, and other environmental toxics (Thompson and Ambrosone, 2006; Reszka et al., 2006). In phase I reaction substrates usually undergo reduction, oxidation, or hydroxylation yielding more polar metabolites; the predominant mediators of this phase are cytochrome P450 (CYP) enzymes (Guengerich, 1999). In most cases phase I metabolism is followed by phase II conjugation reactions. During phase II exogenous or endogenous compounds or their phase I metabolites are conjugated to a more polar molecule, a process that usually produces inactive and water soluble compounds which can be easily excreted by urine or bile (Smith et al., 1994; Turesky, 2004). Conjugating enzymes include glutathione-S-transferases (GSTs), sulfotransferases (SULTs), uridine diphosphate-glucuronosyltransferases (UGTs), N-acetyltransferases (NATs), and Methyltransferases. The combined phase I and II metabolism is mainly a detoxification and elimination process, however, both phases bear the risk of formation of toxic and highly reactive compounds which can induce or promote serious health problems such as cancer (Smith et al., 1994; Windmill et al., 1997). Thus, altered activity of metabolic enzyme holds the potential to increase the exposure to carcinogenic compounds and consequently the risk of tumor formation (Brockstedt et al., 2002).

Moore et al., 2006; Pawlak and Wiebe, 2007). Beyond hormonal factors environmental carcinogens, e.g., tobacco smoke, or genetic factors, e.g., mutations and polymorphisms contribute to breast cancer susceptibility. A genetic basis of breast cancer has been suggested by family studies indicating a two-fold increased risk in the first-degree relatives of women with the disease (Collaborative Group on Hormonal Factors in Breast Cancer, 2001). In the 1990s, the two major breast cancer susceptibility genes BRCA1 and BRCA2 were identified (Miki et al., 1994; Wooster et al., 1995) revealing that harmful mutations in these genes confer to a cumulative disease risk by age 70 years of 65 and 45%, respectively (Antoniou et al., 2003). In the following years further genetic factors with different penetrance and frequency have been described. As of today less than 5% of familial breast cancer were attributed to high penetrance breast cancer genes BRCA1, BRCA2, PTEN, MSH2, STK11, CDH1, and TP53 (Wooster and Weber, 2003; Malone et al., 2006; Walsh et al., 2006) and rare genetic variants at ATM, CHEK2, BRIP, NBN, RAD50, or PALB2 that jointly confer an approximately two-fold increased risk (Meijers-Heijboer et al., 2002; The CHEK2 Breast Cancer Case-Control Consortium, 2004; Rahman et al., 2007). Recent genome-wide association studies revealed strong evidence for more than 18 common breast cancer susceptibility alleles including FGF21, CCND1, TNRC9, MAP3K1, and LSP1 (Cox et al., 2007; Easton et al., 2007; Lambrechts et al., 2012). Most of these genes are related to DNA repair, cell cycle control, apoptosis, cell growth, and division, representing the most important pathways for the protection of cells against carcinogenic processes. However, the lack of observed risk associations with phase I and II enzymes is potentially based on their exclusion from genome-wide association studies due to hampered assay design or poor quality data which is reflected by the low coverage of these genes in current genotyping arrays (Gamazon et al., 2012).
Justenhoven Phase I and phase II enzymes and breast cancer

PHASE I AND II ENZYMES IN ASSOCIATION WITH BREAST CANCER RISK

Candidate gene approaches provide evidence for a particular role of metabolic enzymes in breast carcinogenesis. As of yet only a few studies analyzed the impact of polymorphisms in genes with high sequence homologies, whereas genes like CYP1A1 and CYP1B1 have been studied intensely (Economopoulos and Sergentanis, 2010; Sergentanis and Economopoulos, 2010). Therefore, this review focuses on those genes which are usually underrepresented in association studies due to technical issues. Literature search was done by PubMed using the key words “breast cancer polymorphism phase I,” “breast cancer polymorphism phase II,” “breast cancer polymorphism CYP,” “breast cancer polymorphism UGT,” “breast cancer polymorphism SULT,” “breast cancer polymorphism GST,” and “breast cancer polymorphism NAT” in August 2012. In a next step studies analyzing associations between the respective polymorphisms and breast cancer risk factors or breast tumor characteristics were selected on the basis of study size, i.e., inclusion of more than 500 cases and 500 controls, DNA extracted from blood, validation of genotyping results by an independent method or meta analyses on summary data of at least five independent studies.

Significant associations, with $p < 0.05$ or 95% confidence interval not including 1.0, between polymorphic loci in genes encoding phase I and II enzymes and breast cancer risk are summarized in Table 1. It has been shown that functional genetic variants of the CYP2C19 are associated with overall breast cancer risk and HRT-related breast cancer risk (Gan et al., 2011; Justenhoven et al., 2012). It is of note that these findings in two independent studies show similar effects. The variant CYP2C19*3 (rs57081121) which lead to a decreased activity of the CYP2C19 has been associated
| Subgroup | Ethnicity | Gene | Polymorphism | Nucleotide exchange | Cases | Controls | Odds ratio | p-Value | 95% confidence interval | Reference |
|----------|-----------|------|--------------|---------------------|-------|----------|------------|---------|---------------------|-----------|
| All      | Asian     | CYP2C19 | rs57081211 (*3) | G > A             | 600   | 600      | 2.31       | 0.003   |                     | Gan et al. (2011) |
|          | European  | CYP2C19 | rs6779562    | G > A             | 3139  | 5466     | 1.17       | 0.014   |                     |                       |
|          | Mixed     | UGT1A6  | rs2070599    | A > G             | 3147  | 5484     | 1.22       | 0.007   |                     |                       |
|          | European  | GSTM1   | gene deletion | ins > del          | 1052  | 1098     | 1.88       | 0.12–3.08 |                     | Steck et al. (2007) |
|          | European  | GSTT1   | gene deletion | ins > del          | 541   | 635      | 4.07       | 1.12–14.8 |                     |                       |
|          | European  | GSTP1   | rs1695       | G > A             | 463   | 764      | 1.28       | 0.019   |                     |                       |
| Premenopausal women | European | CYP3A | rs10235235 | T > C             | 4436  | 16393    | 0.91       | 0.03    |                     | Johnson et al. (2012) |
| Premenopausal women | African-American | GSTT1 | rs9282861 | G > A             | 463   | 764      | 1.28       | 0.019   |                     |                       |
| Postmenopausal women | Asian   | SULT1A1 | rs9282861 | G > A             | 1102  | 1147     | 3.6        | 15–8.7  |                     | Yang et al. (2005) |
| Postmenopausal women | European | GSTT1 | gene deletion | del > ins          | 2939  | 5237     | 1.04       | 0.0001  |                     | The MARIE-GENICA Consortium on Genetic Susceptibility for Menopausal Hormone Therapy Related Breast Cancer Risk (2010) |
| Postmenopausal women | European | GSTP1 | rs947894 | C > T             | 2963  | 5269     | 1.25       | 0.022   |                     | The MARIE-GENICA Consortium on Genetic Susceptibility for Menopausal Hormone Therapy Related Breast Cancer Risk (2010) |
| Smoker | European | NAT2   | rs1801280 | T > C             | 4837  | 6017     | 1.5        | 1.2–1.8  |                     | Terry and Goodman (2006) |
| Smoker | European | GSTM1   | gene deletion | ins > del          | 2815  | 3170     | 1.4        | 11–19   |                     | Terry and Goodman (2006) |
| Smoker | European | GSTP1   | rs1138272 | C > T             | 4857  | 6017     | 1.5        | 12–1.41  |                     | Terry and Goodman (2006) |
| Smoker | European | CYP2C9  | rs12241968 (*17) | G > A             | 881   | 911      | 0.71       | 0.01    |                     | Justenhoven et al. (2012) |

Studies with more than 500 breast cancer cases and 500 controls were included.
with increased risk in Asians (Gan et al., 2011) and the variant CYP2C19*17 (rs12248560) causing an ultra rapid metabolizer phenotype leads to a decreased HRT-related breast cancer risk in Europeans (Justenhoven et al., 2012). It is known that CYP2C19 catabolizes estrogens and progesterone (Yamazaki and Shimada, 1997; Cheng et al., 2001; Cribb et al., 2006) and the reported results suggest that increased metabolic activity of the CYP2C19 lowers endogenous hormone levels leading to a decreased risk.

The polymorphism rs10235235 located the non-coding region of the CYP3A locus has been associated with breast cancer risk in premenopausal women (Johnson et al., 2012). It would be of particular interest to follow-up this finding in independent case control collection and functional studies to understand the observed effect of this variant, because other genetic polymorphisms with known functional consequence located in CYP3A4, CYP3A5, CYP3A7, and CYP3A43 showed no association with breast cancer risk (The MARIE-GENICA Consortium on Genetic Susceptibility for Menopausal Hormone Therapy Related Breast Cancer Risk, 2010).

Two functional genetic variants rs6759892 and rs2070959 which are located in the UGT1A6 have been suggested to affect overall breast cancer risk. These variants did not show any association with hormonal factors (The MARIE-GENICA Consortium on Genetic Susceptibility for Menopausal Hormone Therapy Related Breast Cancer Risk, 2010), therefore, the risk effect is may be based on the role of UGT1A6 in the metabolism of exogenous compounds such as potential carcinogenic drug and food ingredients (Harding et al., 1988; Bock and Kohle, 2005).

It has been reported that the deletion of the GSTM1 and GSTT1 gene as well as the variant allele of the GSTP1 rs1695 polymorphism impact overall breast cancer risk (Steck et al, 2007). Subgroup analyses showed an association of the GSTT1 gene deletion and the GSTP1 rs947894 variant with HRT-related breast cancer susceptibility (The MARIE-GENICA Consortium on Genetic Susceptibility for Menopausal Hormone Therapy Related Breast Cancer Risk, 2010). Moreover, the GSTT1 deletion seems to affect breast cancer risk in premenopausal women (Van Emburgh et al., 2008). These observed effects of GST variants on hormone-related tumorigenesis is may be based on decreased conjugation of genotoxic estrogen quinones leading to elevated levels of DNA damage (Strange et al., 2001; Hachey et al., 2003). In addition, the GSTM1 and GSTT1 deletion as well as the GSTP1 rs1138272 variant, were suggested to affect tobacco smoke-related breast cancer risk (Terry and Goodman, 2006) pointing to the potentially critical role of GSTs in the elimination of exogenous carcinogenic compounds such as polycyclic aromatic hydrocarbons (Hayes and Pulford, 1995).

The SULT1A1 rs9282861 polymorphism has been associated with breast cancer risk in postmenopausal women, in particular with BMI > 25 kg/m², suggesting a modifying effect of the variant allele on endogenous sex hormone exposure (Yang et al., 2005; Jiang et al., 2010).

It has been reported that the variant NAT2 alleles rs1801280, rs1799929, rs1208, rs1041983, rs1799930, and rs1799931 lead to an increased smoking-related breast cancer which supports the hypothesis that slow acetylators may suffer greater exposure to tobacco carcinogens (Terry and Goodman, 2006).

**Table 2 | Polymorphisms in phase I and II enzymes associated with histo-pathological characteristics of breast tumor.**

| Subgroup | Ethnicity | Gene | Polymorphism | Nucleotide exchange | Cases | Odds ratio | p-Value | Reference |
|----------|-----------|------|--------------|---------------------|-------|------------|---------|-----------|
| Grading  | Europeans | CYP3A43 | rs61469810 (+2A) | ins > delA          | G1:78 | G > 1:854 | 1.74    | 0.010     | Justenhoven et al. (2010) |
| Node status | Europeans | CYP2C8 | rs1058930 (+4) | G > C              | N0:62 | N > 0:16  | 0.18    | 0.002     | Jernstrom et al. (2009)    |

Studies with more than 500 breast cancer cases and 500 controls were included.

**Phase I and II Enzymes and Breast Tumor Characteristics**

Only a few well designed studies investigated the association between phase I and II enzymes and histo-pathological characteristics of breast tumors (Table 2). One study reported an association between the rs61469810 polymorphism of CYP3A43 (CYP3A43*2A) and poorly differentiated breast tumors which may be explained by a potential contribution of the variant allele to increased sex hormone levels (Justenhoven et al., 2010). Another investigation suggested that the rs1058930 polymorphism of CYP2C8 (CYP2C8*4) affects lymph node status of breast cancer patients (Jernstrom et al., 2009). The variant allele is known to lower metabolic activity of the encoded enzyme, however, the authors stated that an impact of the CYP2C9*2 allele which is in linkage disequilibrium with CYP2C8*4 cannot be excluded (Jernstrom et al., 2009).

**Conclusion**

Genetic variations of phase I and II enzymes alter their activity or protein biosynthesis leading to defective detoxification and elimination of carcinogenic compounds. Due to a high degree of DNA sequence similarity among genes of subfamilies accurate genotyping requires elaborated methods and exhaustive quality control. Until now a few well designed studies give insights into the effect of polymorphisms in metabolic enzymes on breast cancer risk and point to their crucial action in steroid hormone catabolism. These finding underline the pivotal role of sex hormones in the regulation of proliferation, differentiation, and apoptosis as critical pathways for onset and progression of breast cancer (Schindler et al., 1998; Gruber et al., 2002; Seeger et al., 2003; Gadducci et al., 2005). However, a usual short coming is the publication bias related to findings without significant effect. Taken together, the prediction of breast cancer risk on polymorphisms of phase I and II enzymes is in its initial stage and prospective studies including different ethnic groups are needed in order to achieve genotyping based reliable risk determination. Recent developments of gene panels and arrays provide the technical basis for further assessment of the impact of variations in metabolic genes as well as gene–gene and gene-exposure interactions. Overall, comprehensive investigations of multiple genetic, endogenous, and exogenous factors...
will promote the understanding of the molecular mechanisms of breast carcinogenesis and support the improvement of prevention strategies.

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