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EPIDEMIOLOGY

*CYP2C19**17 is associated with decreased breast cancer risk

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Abstract Cytochrome P450 2C19 (CYP2C19) plays an important role in the metabolism of xenobiotics and drugs and contributes to the catabolism of endogenous substrates like estradiol. Genetic variability impacts expression and activity of CYP2C19 and therefore can influence catabolism of estrogens. In the present study we analyzed the association of three polymorphisms of *CYP2C19* namely *CYP2C19**2 (CY*P2C19*_681_G>A, rs4244285), *CYP2C19**3 (*CYP2C19*_636_G>A, rs57081121) and *CYP2C19**17 (*CYP2C19*_-806_C>T, rs12248560), with breast cancer susceptibility. We genotyped 1,015 breast cancer cases and 1,021 age-matched, population-based controls of the German GENICA study by matrix assisted laser desorption/ionization time-of-flight mass spectrometry. Risk estimates were calculated by logistic regression. All tests were two-sided. We observed a decreased breast cancer risk for carriers of the *CYP2C19**17 allele (OR 0.77, 95% CI: 0.65–0.93; $P = 0.005$). In subgroup analysis we observed a significant decreased breast cancer risk for women using hormone therapy for ten years or longer who were carriers of the *CYP2C19**17 allele (OR 0.57, 95% CI: 0.39–0.83; $P = 0.003$). Since *CYP2C19**17 defines an ultra rapid metabolizer phenotype we suggest that an increased catabolism of estrogens by CYP2C19 may lead to decreased estrogen levels and therefore reduces breast cancer risk. This protective effect seems to be stronger in combination with long-term intake of supplemental estrogens during hormone therapy.

Keywords CYP2C19 · Polymorphisms · Breast cancer · Hormone therapy

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Introduction

Increased estrogen levels are a known risk factor for breast cancer [1]. They can result from variations 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. So far, conflicting results have been reported from association studies [2] and a recent multigene approach showed that none of the 18 polymorphisms residing in 11 genes of the estrogen metabolic pathway (*CYP17A1*,

CYP19A1, *EPHX1*, *HSD17B1*, *SRD5A2*, *PPARG2*, *CYP1A1*, *CYP1B1*, *COMT*, *GSTP1* and *SOD2*) was associated with breast cancer risk [3]. The cytochrome P450 enzyme (CYP) 2C19 catalyzes the 17 beta-hydroxy dehydrogenation [4] and 16 alpha-hydroxylation [5] of estradiol. However, not much attention has been paid so far to explore a possible relationship between *CYP2C19* polymorphisms and breast cancer risk. Rather, CYP2C19 has moved to center stage because of its prominent role in the metabolism of the majority of clinically used drugs including proton pump inhibitors (PPI) [6–9], antidepressants [10] and antiestrogens [11]. Approximately 30–40% of all drugs in clinical use are metabolized by CYP2C19, CYP2D6 and CYP2C9. Importantly, there are known CYP2C19 genotype phenotype relationships which are based on the discovery of poor metabolizer (PM) and extensive metabolizer (EM) phenotypes for the substrate 4-hydroxylate-S-mephenytoin [12] which have been assigned to genetic polymorphisms. There are three CYP2C19 metabolizer phenotypes of which EM is assigned to the *CYP2C19**1 allele with a frequency of 84% in Caucasians [13]. PM mainly result from *CYP2C19**2 (*CYP2C19*_681_G>A) located in exon 5 causing a splicing defect and leading to abrogated CYP2C19 activity with a frequency of approximately 15% [13–15]. Very rarely, PM result from *CYP2C19**3 (*CYP2C19*_636_G>A) located in exon 4 and causing a premature stop codon [13, 14]. A third ultra rapid metabolizer (UM) phenotype recently has been recognized based on the observation of variations of drug response in EM individuals which lead to the discovery of the *17 allele (*CYP2C19*_-806_C>T) in the *CYP2C19* promoter region [16]. In the case of breast cancer the CYP2C19 UM has attracted attention as a treatment predictor of the response to tamoxifen, a common antiestrogen for the treatment of hormone sensitive postmenopausal breast cancer. In particular, the *CYP2C19**17 allele has been shown to predict the risk of breast cancer recurrence [11] in that carriers of the *CYP2C19**17 allele had less frequent recurrences following tamoxifen when compared with non *CYP2C19**17 carriers. This finding has been explained by the UM phenotype inherent to this allele to effectively convert tamoxifen to clinically potent metabolites [8]. Similar relationships have been observed with respect to the therapeutic outcome of PPI treatment of acid related gastrointestinal disorders such as gastric ulcers and gastroesophageal reflux disease [6–9].

In the light of the *CYP2C19**17 defining a clinically important phenotype it is now important to clarify whether *CYP2C19* polymorphisms also play a role in breast cancer risk. Here we report on the investigation of an association between *CYP2C19* polymorphisms (*CYP2C19**2, *CYP2C19**3 and *CYP2C19**17) and breast cancer risk in the German population-based, age-matched breast cancer case-control study GENICA and show a protective role of the *CYP2C19**17 polymorphism in the risk to develop breast cancer.

Material and methods

Study population

The GENICA study participants of the population-based breast cancer case-control study from the Greater Bonn Region, Germany, were recruited between 08/2000 and 09/2004 as described previously [17–19]. In brief, there are 1,143 incident breast cancer cases and 1,155 population controls matched in 5-year classes. Cases and controls were eligible if they were of Caucasian ethnicity, current residents of the study region and below 80 years of age. Information on known and supposed risk factors was collected for all participants via in-person interviews. The response rate for cases was 88% and for controls 67%. Characteristics of the study population regarding potential breast cancer risk factors include age at diagnosis (<50, ≥50 years), menopausal status (premenopausal, postmenopausal), family history of at least one first degree relative with breast or ovarian cancer (yes, no), use of oral contraceptives (never, >0–<5, 5–<10, ≥10 years), use of hormone therapy (never, >0–<10, ≥10 years), body mass index (<20, 20–<25, 25–<30, ≥30 kg/m^2) and smoking status (never, former, current) (Table 1).

The GENICA study was approved by the Ethic's Committee of the University of Bonn. All study participants gave written informed consent.

Isolation of DNA and genotyping

Genomic DNA was extracted from heparinized blood samples (Puregene^{TM}, Gentra Systems, Inc., Mineapolis, USA) as previously described [17]. DNA samples were available for 1,021 cases (89%) and 1,015 controls (88%). The polymorphisms *CYP2C19*_-806_C>T (*CYP2C19**17, rs12248560), *CYP2C19*_681_G>A (*CYP2C19**2, rs4244285) and *CYP2C19*_636_G>A (*CYP2C19**3, rs57081121) were subjected to genotyping of all 2,036 DNA samples. Genotyping was performed by matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) as described previously [11, 17]. A Sequenom Compact MALDI-TOF MS was used for data acquisitions from the SpectroCHIP. Genotyping calls were made with MASSARRAY RT software v 3.0.0.4 (Sequenom, San Diego, CA, USA). For quality control repeated analyses were performed for 20% randomly selected samples. Primers were synthesized by Metabion International AG, Martinsried, Germany, sequences are available on request.

Table 1 Epidemiologic baseline information of the GENICA study population

	Cases *n* (%)	Controls *n* (%)	OR[a] (95% CI)
Age (years)			
<50	225 (22.6)	226 (22.3)	
≥50	796 (77.3)	789 (77.7)	
Menopausal status			
Pre	248 (24.8)	235 (23.6)	1.00[b]
Post	753 (75.2)	762 (76.4)	0.90 (0.65–1.24)
Family history of breast cancer			
No	845 (84.4)	914 (91.7)	1.00[b]
Yes	156 (15.6)	83 (8.3)	**2.04 (1.53–2.70)**[c]
Use of oral contraceptives (years)			
Never	372 (36.5)	368 (36.3)	1.00[b]
> 0 < 5	180 (17.7)	185 (18.3)	0.97 (0.74–1.28)
5 < 10	134 (13.1)	120 (11.8)	1.11 (0.81–1.52)
≥10	333 (32.7)	340 (33.6)	0.97 (0.76–1.25)
Use of hormone therapy (years)			
Never	506 (49.8)	509 (50.3)	1.00[b]
> 0 < 10	245 (24.1)	290 (28.6)	0.86 (0.68–1.09)
≥10	266 (26.1)	214 (21.1)	1.36 (1.05–1.76)
Body mass index (kg/m^2)			
<20	88 (8.8)	70 (7.2)	1.28 (0.91–1.81)
20 < 25	459 (45.9)	464 (46.4)	1.00[b]
25 < 30	302 (30.1)	319 (32.0)	0.99 (0.80–1.22)
≥30	152 (15.2)	144 (14.4)	1.08 (0.83–1.42)
Smoking			
Never	586 (57.5)	555 (54.7)	1.00[b]
Former	192 (18.8)	215 (21.2)	0.95 (0.75–1.19)
Current	242 (23.7)	245 (24.1)	0.84 (0.66–1.06)

The table includes all patients for whom genomic DNA was available

[a] OR conditional on age in 5-year groups adjusted for menopausal status, family history of breast cancer, use of oral contraceptives, use of hormone therapy, body mass index and smoking

[b] Reference

[c] $P < 0.001$

CI, Confidence interval; OR, odds ratio

Statistical analyses

CYP2C19 genotype frequencies were tested for Hardy–Weinberg equilibrium. Associations between genetic variables and breast cancer risk were analyzed by conditional logistic regression adjusted for six potential epidemiological breast cancer risk factors (menopausal status, family history of breast cancer, use of oral contraceptives, use of hormone therapy, body mass index and smoking). Subgroup analyses were performed for these six epidemiological variables. To correct for multiple testing we divided the significance level of 0.05 by the number of tested variables. In case of epidemiological variables 0.05 was divided by six and thus *P*-values < 0.008 were considered significant. Risk estimates were given as odds ratios (OR) and 95% confidence interval (CI). Statistical analyses were done using SAS v 9.1.3 (SAS Institute Inc., Cary, NC, USA) and *CYP2C19* haplotype frequencies were estimated using Haploview [20].

Results

We analyzed *CYP2C19**2, *CYP2C19**3 and *CYP2C19**17 alleles using MALDI-TOF MS. Call rates were >98% and repeated analyses of 20% of randomly selected samples showed 100% concordance. Genotype frequencies of cases and controls met Hardy–Weinberg equilibrium. Minor allele frequency of *CYP2C19**2 and *CYP2C19**17 were 14 and 25%, respectively. No *CYP2C19**3 allele was detected and therefore it was excluded from further statistical analyses.

In single factor analysis we observed a decreased breast cancer risk for heterozygous and homozygous carriers of *CYP2C19**17 allele (OR 0.80, 95% CI: 0.66–0.97; $P = 0.021$ and OR 0.64, 95% CI: 0.44–0.94; $P = 0.024$, respectively, Table 2). Significance of these results vanished following correction for multiple testing. Combined genotypes including heterozygous and homozygous carriers of *CYP2C19**17 showed a significant decreased breast cancer risk (OR 0.77, 95% CI: 0.65–0.93; $P = 0.005$, Table 2). In subgroup analyses we observed a significant decrease of breast cancer risk for women using hormone therapy for 10 years or longer who were heterozygous for *CYP2C19**17 (OR 0.54, 95% CI: 0.36–0.80; $P = 0.002$, Table 3) or who were carriers of at least one *CYP2C19**17 allele (OR 0.57, 95% CI: 0.39–0.83; $P = 0.004$, Table 3). No other subgroups showed any significant risk association for *CYP2C19**17 (data not shown). For *CYP2C19**2 we observed no risk associations neither in single factor analysis (Table 2) nor in subgroup analyses (data not shown).

Haplotype analysis showed that *CYP2C19**17 and *CYP2C19**2 are in linkage disequilibrium ($D' = 0.98$, r-squared = 0.05). The haplotype comprising *CYP2C19**17 shows a significantly decreased breast cancer risk (OR 0.81, 95% CI: 0.70–0.95; $P = 0.008$, Table 4). Combined genotypes showed a borderline risk association for women who were heterozygous for both *CYP2C19**17 and *CYP2C19**2 (OR 0.65, 95% CI: 0.45–0.93; $P = 0.024$, Table 4). Significance of this finding vanished following correction for multiple testing.

Discussion

In the present study we analyzed three functional relevant variations of *CYP2C19* namely *CYP2C19**17, *CYP2C19**2

Table 2 Genotype frequencies of *CYP2C19**17 and *CYP2C19**2 in breast cancer cases and controls and estimated risks

Polymorphism	Genotypes	Cases *n* (%)	Controls *n* (%)	OR[a] (95% CI)
*CYP2C19**17	CC	624 (62.9)	565 (56.7)	1.00[b]
(*CYP2C19*_-806_C>T)	CT	319 (32.1)	362 (36.4)	**0.80 (0.66–0.97)**[c]
	TT	50 (5.0)	69 (6.9)	**0.64 (0.44–0.94)**[d]
	CT + TT	369	431	**0.77 (0.65–0.93)**[e]
*CYP2C19**2	GG	707 (73.0)	728 (73.5)	1.00[b]
(*CYP2C19*_681_G>A)	GA	236 (24.3)	244 (24.6)	1.00 (0.81–1.23)
	AA	26 (2.7)	19 (1.9)	1.39 (0.76–2.54)
	GA + AA	262	263	1.03 (0.84–1.26)

[a] OR conditional on age in 5-year classes, adjusted for menopausal status, family history of breast cancer, use of oral contraceptives, use of hormone therapy, body mass index and smoking

[b] Reference

[c] $P = 0.021$

[d] $P = 0.024$

[e] $P = 0.005$

CI, Confidence interval; OR, odds ratio

Table 3 Genotype frequencies of *CYP2C19**17 in breast cancer cases and controls in the subgroup of women using hormone therapy for 10 years or longer

	Genotype	Cases *n* (%)	Controls *n* (%)	OR[a] (95% CI)
*CYP2C19*_-806_C>T	CC	177 (66.8)	113 (53.8)	1.00[b]
(*CYP2C19**17)	CT	75 (28.3)	87 (41.4)	**0.54 (0.36–0.80)**[c]
	TT	13 (4.9)	10 (4.8)	0.86 (0.36–2.05)[d]
	CT + TT	88	97	**0.57 (0.39–0.83)**[e]

[a] OR conditional on age in 5-year classes, adjusted for menopausal status, family history of breast cancer, use of oral contraceptives, body mass index and smoking

[b] Reference

[c] $P = 0.002$

[d] $P = 0.731$

[e] $P = 0.004$

CI, Confidence interval; OR, odds ratio

and *CYP2C19**3 and their impact on breast cancer risk. We chose to investigate *CYP2C19* and its known common functional polymorphisms because the available literature indicated that their potential contribution to breast cancer susceptibility has not been addressed in sufficient detail. We observed a significant association between *CYP2C19**17 [16] and decreased breast cancer risk (OR 0.77), in that women with *17 alleles had an up to 23% lower risk when compared with women carrying the reference allele.

The *CYP2C19**17 gene variant has recently been identified within the context of therapeutic failure in the drug treatment with PPI and antidepressants [16]. This was possible because it had been noticed that despite the good correlation of pharmacokinetic and acid inhibitory effects with EM and PM genotypes there was a marked variation in CYP2C19 activity among EMs. A detailed sequencing approach of the CYP2C19 promoter region finally revealed the *CYP2C19**17 allele with rapid CYP2C19 activity in populations of different ethnic origin [16]. In vitro and in vivo studies showed that the *CYP2C19**17 mediated UM phenotype is apparently caused by an increased transcription rate [16, 21]. It has been concluded that the existence of the *CYP2C19**17 allele is likely to explain why some patients exhibit a lack of response to commonly prescribed dosages of certain PPI and antidepressants, because of an unusually rapid clearance of these [16]. This unraveled genotype phenotype relationship lends support to our observation of a protective effect of the *CYP2C19**17 for the risk to develop breast cancer. Since CYP2C19 catalyzes the 17 beta-hydroxy dehydrogenation [4] and 16 alpha-hydroxylation [5] within estrogen metabolism it is conceivable that a *CYP2C19**17 predisposing UM phenotype

Table 4 *CYP2C19**17 and *CYP2C19**2 haplotype frequencies and frequencies of combined genotypes in breast cancer cases and controls

CYP2C19		Cases	Controls	OR (95% CI)
*17 (-806_C>T)	*2 (681_G>A)	*n* (%)	*n* (%)	
Haplotypes				
C	G	1,252 (63.7)	1,220 (60.6)	1.00[a]
C	A	290 (14.8)	288 (14.3)	0.98 (0.82–1.18)
T	G	422 (21.5)	506 (25.1)	**0.81 (0.70–0.95)**[b]
T	A	–	–	–
Combined genotypes				
CC	GG	403 (41.0)	386 (38.3)	1.00[b]
CC	GA	182 (18.5)	165 (16.4)	1.06 (0.82–1.36)
CC	AA	26 (2.6)	20 (2.0)	1.25 (0.68–2.27)
CT	GG	264 (26.9)	283 (28.1)	0.89 (0.72–1.11)
CT	GA	56 (5.7)	83 (8.2)	**0.65 (0.45–0.93)**[c]
CT	AA	0 (0)	0 (0)	–
TT	GG	51 (5.2)	70 (7.0)	0.71 (0.47–1.03)
TT	GA	1 (0.1)	0 (0)	–
TT	AA	0 (0)	0 (0)	–

[a] Reference

[b] $P = 0.008$

[c] $P = 0.024$

CI, Confidence interval; OR, odds ratio

may protect from breast cancer due to decrease of estrogen levels. This interpretation draws further substance from the results of our subgroup analysis of postmenopausal women previously exposed to exogenous estrogens during hormone therapy. In particular, women who used hormone therapy for more than 10 years had an even more pronounced reduction of breast cancer risk of more than 40% when they were carriers of the *CYP2C19**17 allele (OR 0.57). This finding is of special interest because it seems to counterbalance the known breast cancer risk effects associated with an elevated estrogen exposure during long-term hormone therapy that have been reported in large international studies [22, 23]. Importantly, this hormone therapy associated breast cancer risk was also observed in our GENICA breast cancer case-control collection [19] of which we now report the *CYP2C19**17 breast cancer protective effect. Because a *CYP2C19**17 predisposing UM phenotype may protect from breast cancer via rapid degradation of estrogens we suggest that this polymorphism should be further explored as a potential breast cancer prevention factor in large international breast cancer case-control studies. The follow-up of this issue is particularly important for women in need for hormone therapy for the relief of postmenopausal symptoms who may benefit from up-front *CYP2C19* genotyping prior to hormone intake. Such investigations might be considered an important step towards an educated use of hormone therapy and better management of postmenopausal hormone prescription.

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