Three polymorphisms in cytochrome P450 1B1 (CYP1B1) gene and breast cancer risk: a meta-analysis

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Breast Cancer Res Treat (2010) 122:545–551
DOI 10.1007/s10549-009-0728-z

EPIDEMIOLOGY

Three polymorphisms in cytochrome P450 1B1 (CYP1B1) gene and breast cancer risk: a meta-analysis

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Received: 28 December 2009 / Accepted: 30 December 2009 / Published online: 7 January 2010

Abstract Cytochrome P450 1B1 (CYP1B1) is a P450 enzyme implicated in the metabolism of exogenous and endogenous substrates. The metabolism of polycyclic aromatic hydrocarbons and other procarcinogens through CYP1B1 may well lead to their activation. Apart from the extensively studied Val432Leu polymorphism, three single nucleotide polymorphisms in CYP1B1 have been studied concerning their potential implication in terms of breast cancer risk: Arg48Gly, Ala119Ser and Asn453Ser. This meta-analysis aims to examine whether the three aforementioned polymorphisms are associated with breast cancer risk. Eligible articles were identified by a search of MEDLINE bibliographical database for the period up to December 2009. Concerning Arg48Gly polymorphism, 10 studies were eligible (11,321 cases and 13,379 controls); 11 studies were eligible for Ala119Ser (10,715 cases and 11,678 controls); 12 cases were eligible regarding Asn453Ser (11,630 cases and 14,053 controls). Pooled odds ratios (OR) were appropriately derived form fixed-effects or random-effects models. Sensitivity analysis excluding studies whose genotype frequencies in controls significantly deviated from Hardy–Weinberg equilibrium was performed. Concerning Arg48Gly, the pooled ORs (95% CI) were 0.933 (0.808–1.078) for heterozygous and 0.819 (0.610–1.100) for homozygous Gly subjects. Regarding Ala119Ser, the pooled ORs were 0.992 (0.896–1.097) for heterozygous and 0.935 (0.729–1.198) for homozygous Ser subjects. With respect to Asn453Ser, the pooled ORs were 0.961 (0.906–1.019) for heterozygous and 0.984 (0.846–1.144) for homozygous Ser subjects. In conclusion, this meta-analysis suggests that CYP1B1 Arg48Gly, Ala119Ser and Asn453Ser polymorphisms are not associated with breast cancer risk. Studies on Chinese populations are needed, to elucidate race-specific effects on East Asian populations, if any.

Keywords CYP1B1 · Cytochrome P450 · Polymorphism · Breast cancer · Arg48Gly · Ala119Ser · Asn453Ser

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Introduction

Cytochrome P450 1B1 (CYP1B1) is a key P450 enzyme implicated in the metabolism of exogenous and endogenous substrates [1]. A variety of studies have demonstrated that the metabolism of polycyclic aromatic hydrocarbons and other procarcinogens through CYP1B1 may well lead to the activation of the carcinogenic compounds [2, 3]. It is worth mentioning that, among endogenous substrates, CYP1B1 is implicated in the metabolism of oestrogen [4]; interestingly, women exhibit higher expression of CYP1B1 than men [5].

CYP1B1 is a polymorphic gene in the human population; the genotype frequencies have been studied with respect to a variety of cancer types, including breast cancer. At a meta-analytical level, attention has been drawn upon the most extensively studied CYP1B1 polymorphism, i.e. Val432Leu and breast cancer risk [6]. Nevertheless, three additional polymorphisms have been located within CYP1B1: Arg48Gly, Ala119Ser and Asn453Ser. Importantly, these polymorphic variants have been associated with enhanced catalytic activity when compared to the

wild-type allele [7, 8]; it has been postulated that this functional finding may confer susceptibility towards breast cancer at a certain extent [8].

Despite the importance of the three CYP1B1 polymorphisms above, the most recent meta-analysis on their possible association with breast cancer has appeared in 2005, examining Ala119Ser and Asn453Ser and including four and three studies, respectively [9]. Nevertheless, since then a considerable amount of data have appeared concerning Ala119 Ser (8 case–control studies) and Asn453Ser (7 case–control studies). It seems also worth declaring that, to our knowledge no meta-analysis has appeared on the possible association between CYP1B1 Arg48Gly and breast cancer risk.

Under the light of the above, the need for an up-to-date, comprehensive meta-analysis has become evident. This meta-analysis aims to examine whether the genotype status of Arg48Gly, Ala119Ser and Asn453Ser polymorphisms in CYP1B1 gene is associated with breast cancer risk.

Methods

Eligible studies and data abstraction

Eligible articles were identified by a search of MEDLINE bibliographical database for the period up to December 2009 (last search: 15 December 2009) using combinations of the following keywords: 'breast', 'cancer', 'CYP1B1', 'cytochrome P-450' or 'cytochrome P450', 'polymorphism', 'Arg48Gly', 'Ala119Ser', 'Asn453Ser', 'codon 48', 'codon 119' and 'codon 453'. In addition, we checked all the references of relevant reviews and eligible articles that our search retrieved. Language restrictions were not used and two investigators (KPE and TNS), working independently, searched the literature and extracted data from each eligible case–control study.

All case–control studies with any sample size examining the association between the four examined polymorphisms and breast cancer (i.e. reporting the genotype frequencies in cases and controls, respectively) were considered eligible for this analysis. For each of the eligible case–control studies the following data were collected: journal name, year of publication, inclusion and exclusion criteria, demographic characteristics of the population being studied, frequencies of genotypes in cases and controls. Studies not designed as case–control, systematic reviews and studies with mutually overlapping populations were excluded from this meta-analysis.

Statistics

Based on the genotype frequencies in cases and controls, crude odds ratios (OR) as well as their standard errors (SE) were calculated. For each polymorphism, four different ORs were calculated: (i) heterozygous carriers versus 'wild type', (ii) homozygous carriers versus 'wild type', (iii) dominant model, i.e. heterozygous and homozygous carriers grouped together versus wild type and (iv) recessive model, i.e. homozygous carriers versus 'wild type' and heterozygous carriers grouped together. Separate race-specific analyses were considered in case relevant data existed, according to the algorithm adopted in our previous meta-analyses [10–14]. In case of zero cells, an appropriate continuity correction (addition of 0.5) was implemented [10].

The fixed-effects model (Mantel–Haenszel method), or the random effects (DerSimonian Laird) model, were appropriately used to calculate the pooled OR. Between-study heterogeneity and between-study inconsistency were assessed by using Cochran Q statistic and by estimating I^2, respectively [15]. In case significant heterogeneity was detected, the random effects model was chosen. Meta-analysis was performed using the 'metan' STATA command.

Evidence of publication bias was determined using Egger's [16] formal statistical test and by visual inspection of the funnel plot. For the interpretation of Egger's test, statistical significance was defined as $P < 0.1$. The Egger's test was performed using the 'metabias' STATA command. In addition, meta-regression was performed to assess whether Odds Ratio (OR) was associated with publication year. Meta-regression was performed with the 'metareg' STATA command.

Moreover, sensitivity analysis was performed excluding studies whose allele frequencies in controls exhibited significant deviation from the Hardy–Weinberg Equilibrium (HWE), given that the deviation may denote bias. For the assessment of the deviation from HWE, the appropriate goodness-of-fit chi-square test was performed [17, 18]. For the interpretation of the goodness-of-fit chi-square test, statistical significance was defined as $P < 0.05$. Analyses were conducted using STATA 10.0 (STATA Corp., College Station, TX, USA).

Results

Eligible studies

Out of the 73 abstracts retrieved through the search criteria, 47 were irrelevant, three articles [19–21] were excluded because they were conducted on overlapping populations with other eligible studies [22, 23] (these excluded articles represent smaller studies performed on subsets of larger eligible studies), two articles [24, 25] were excluded given that they have not included breast cancer cases in their study design, one article [26] was excluded given that it has

not included controls in its study design, and one study was excluded due to reporting reasons [27], i.e. no reporting of the relevant genotype frequencies.

Concerning Arg48Gly polymorphism, 10 studies were eligible (11,321 cases and 13,379 controls) [9, 22, 23, 28–33]; 11 studies were eligible for Ala119Ser (10,715 cases and 11,678 controls) [9, 22, 23, 28, 31, 34–38]; 12 cases were eligible regarding Asn453Ser (11,630 cases and 14,053 controls) [22, 29–32, 35, 39–43].

Arg48Gly polymorphism

The pooled ORs along with their 95% CIs are presented in the Table 1; no significant associations were demonstrated. The forest plots are depicted in Fig. 1.

No race-specific analysis was performed, as all studies pertained exclusively to Caucasian populations, except for solely two on Chinese subjects [9, 33] and one study part on mixed populations [33].

Regarding the overall analysis, publication bias was not detected at the analysis on heterozygous carriers ($P = 0.208$) and the dominant model ($P = 0.133$); on the other hand, evidence of publication bias was detected at the analysis on homozygous carriers ($P = 0.072$) and at the recessive model ($P = 0.061$). Meta-regression with publication year did not point to any significant modifying role upon the effect of Arg48Gly either at the Arg/Gly versus Arg/Arg comparison ($P = 0.213$), Gly/Gly versus Arg/Arg comparison ($P = 0.172$), the dominant model ($P = 0.156$) or the recessive model ($P = 0.119$).

Examining genotype frequencies in controls, significant deviation from HWE was detected in one study [30]. After the exclusion of the study significantly departing from HWE the results remained practically unchanged. Specifically, the pooled ORs were as follows: 0.908 (0.761–1.084, random effects) for heterozygous carriers, 0.762 (0.522–1.112, random effects) for homozygous carriers, 0.905 (0.762–1.074, random effects) for the dominant model and 0.892 (0.688–1.157, random effects) for the recessive model. Worthy of note, the deviation from HWE could not be assessed due to reporting reasons in one study [32].

Ala119Ser polymorphism

The pooled ORs along with their 95% CIs are presented in detail in the Table 1; no significant associations were demonstrated. The respective forest plots are depicted in Fig. 2. Once again, no race-specific meta-analysis was performed, as solely one study [37] was conducted on African populations, whereas solely two studies [9, 34] were performed on Chinese populations.

Concerning the overall analysis, publication bias was not detected at the analysis on heterozygous carriers ($P = 0.237$) and the dominant model ($P = 0.117$); on the other hand, significant publication bias was demonstrated at the analysis on homozygous carriers ($P = 0.047$), and marginally at the recessive model ($P = 0.091$). Meta-regression with publication year did not point to any significant modifying role upon the effect of Ala119Ser, either at the Ala/Ser versus Ala/Ala comparison ($P = 0.481$), Ser/Ser versus Ala/Ala comparison ($P = 0.252$), the dominant model ($P = 0.590$) or the recessive model ($P = 0.124$).

Examining genotype frequencies in controls, significant deviation from HWE was detected in one study, i.e. the Caucasian part of the study by Gulyaeva et al. [36]. After the exclusion of this study the results remained practically unchanged, as the associations still did not reach significance. Specifically, the pooled ORs were as follows: 0.994 (0.895–1.104, random effects) for heterozygous carriers, 0.973 (0.761–1.244, random effects) for homozygous carriers, 1.001 (0.894–1.121, random effects) for the dominant model and 1.035 (0.841–1.272, random effects) for the recessive model.

Table 1 Pooled ORs by race for heterozygous, homozygous carriers, dominant and recessive model for the examined polymorphisms

Polymorphisms	Heterozygous[a]		Homozygous[b]		Dominant model[c]		Recessive model[d]	
	OR (95% CI)	Test for heterogeneity	OR (95% CI)	Test for heterogeneity	OR (95% CI)	Test for heterogeneity	OR (95% CI)	Test for heterogeneity
Arg48Gly ($n = 10$)	0.933 (0.808–1.078)	$P < 0.001$	0.819 (0.610–1.100)	$P < 0.001$	0.929 (0.806–1.071)	$P < 0.001$	0.930 (0.759–1.140)	$P = 0.001$
Ala119Ser ($n = 11$)	0.992 (0.896–1.097)	$P = 0.015$	0.935 (0.729–1.198)	$P < 0.001$	0.990 (0.885–1.107)	$P = 0.001$	1.001 (0.811–1.237)	$P < 0.001$
Asn453Ser ($n = 12$)	0.961 (0.906–1.019)[F]	$P = 0.336$	0.984 (0.846–1.144)[F]	$P = 0.751$	0.968 (0.915–1.023)[F]	$P = 0.197$	0.996 (0.858–1.157)[F]	$P = 0.849$

All pooled ORs were derived from random-effects models except for cells marked with [F] (fixed)

[a] For Arg48Gly: Arg/Gly vs. Arg/Arg; For Ala119Ser: Ala/Ser vs. Ala/Ala; For Asn453Ser: Asn/Ser vs. Asn/Asn

[b] For Arg48Gly: Gly/Gly vs. Arg/Arg; For Ala119Ser: Ser/Ser vs. Ala/Ala; For Asn453Ser: Ser/Ser vs. Asn/Asn

[c] For Arg48Gly: Gly/Gly and Arg/Gly vs. Arg/Arg; For Ala119Ser: Ser/Ser and Ala/Ser vs. Ala/Ala; For Asn453Ser: Ser/Ser and Asn/Ser vs. Asn/Asn

[d] For Arg48Gly: Gly/Gly vs. Arg/Arg and Arg/Gly; For Ala119Ser: Ser/Ser vs. Ala/Ala and Ala/Ser; For Asn453Ser: Ser/Ser vs. Asn/Asn and Asn/Ser

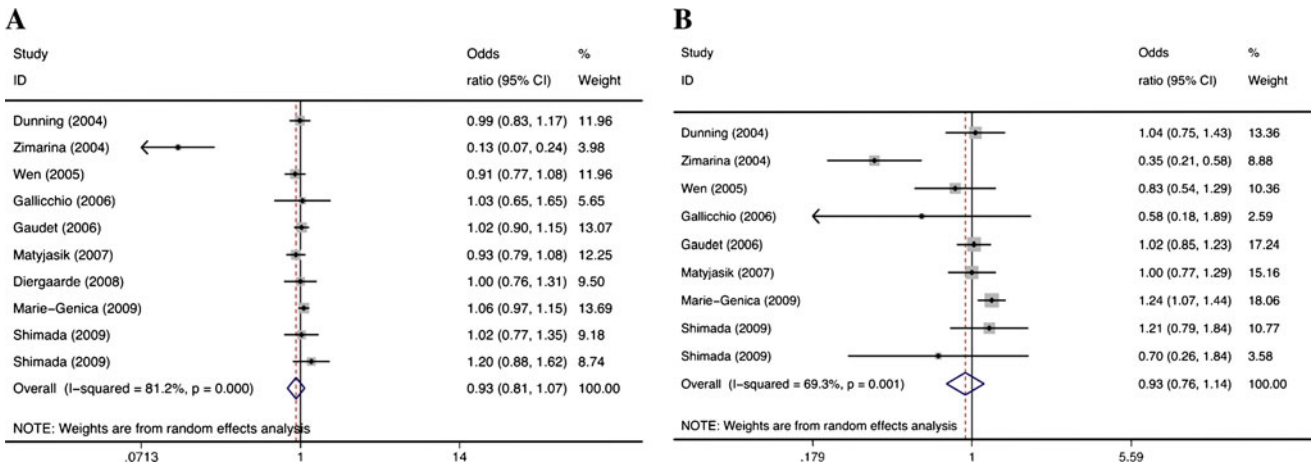

Fig. 1 Forest plot for the overall association between Arg48Gly polymorphism and breast cancer risk for the **a** dominant and **b** recessive model. Each study is shown by the point estimate of the Odds Ratio (OR) (the size of the square is proportional to the weight of each study) and 95% confidence interval for the OR (extending lines). The pooled OR and 95% confidence interval have been appropriately derived from random effects model

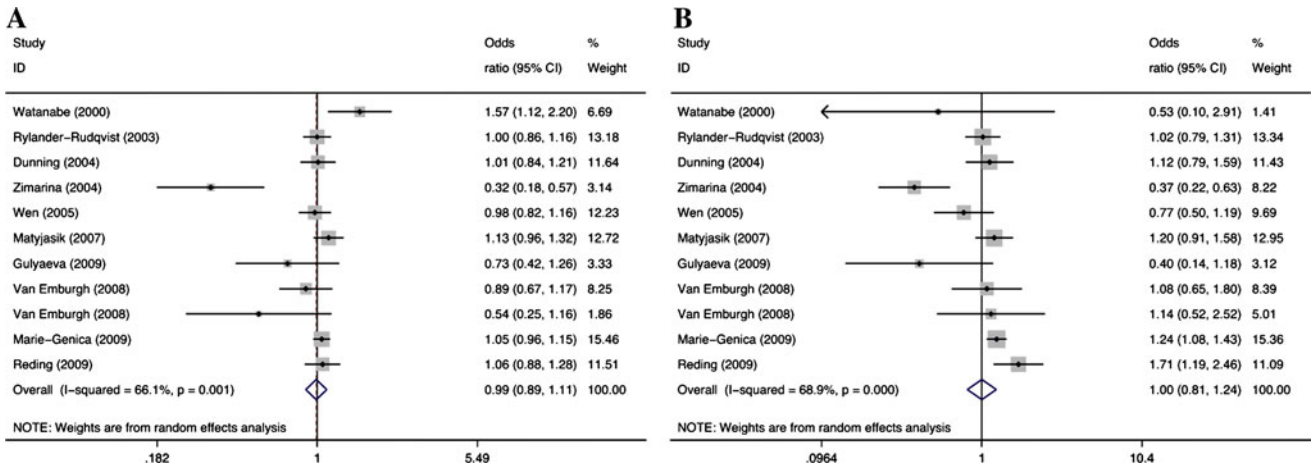

Fig. 2 Forest plot for the overall association between Ala119Ser polymorphism and breast cancer risk for the **a** dominant and **b** recessive model (random effects)

Asn453Ser polymorphism

The pooled ORs along with their 95% CIs are presented detail in the Table 1; no significant association was demonstrated. No race-specific analysis was performed, as all studies except for two (one on African Americans [39] and one on mixed populations [42] pertained exclusively to Caucasian populations. The forest plots are depicted in Fig. 3.

Publication bias was not detected at the analysis on homozygous carriers ($P = 0.246$) and at the recessive model ($P = 0.319$); on the contrary, publication bias became evident at the analysis on heterozygous carriers ($P = 0.077$) and the dominant model ($P = 0.050$). Meta-regression with publication year did not point to any significant modifying role upon the effect of Asn453Ser, either at the Asn/Ser versus Asn/Asn comparison ($P = 0.760$), Ser/Ser versus Asn/Asn comparison ($P = 0.943$), the dominant model ($P = 0.883$) or the recessive model ($P = 0.885$).

The examination of genotype frequencies in controls did not point to any significant deviation from HWE. It is worth mentioning, however, that in one study [32] the deviation from HWE could not be assessed due to reporting reasons, i.e. categories of genotypes merged in the individual studies.

Discussion

The principal message of this meta-analysis is the lack of association between CYP1B1 Arg48Gly, Ala119Ser and

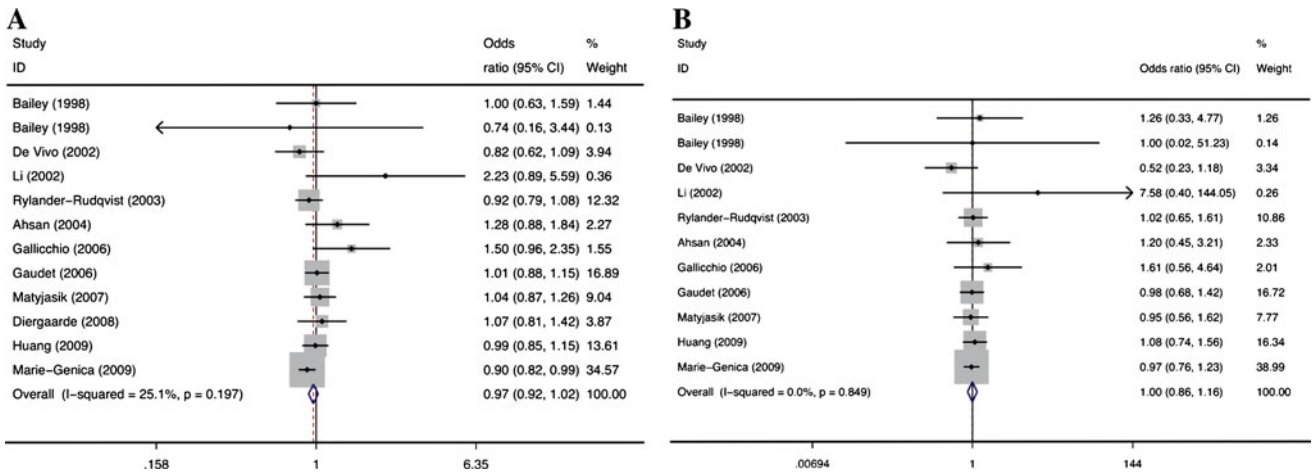

Fig. 3 Forest plot for the overall association between Asn453Ser polymorphism and breast cancer risk for the **a** dominant and **b** recessive model (fixed effects)

Asn453Ser polymorphisms and breast cancer risk. This seems of particular importance, as the present meta-analysis does not confirm the theoretical envisagement based on the catalytical properties of the variants, according to which the enhanced catalytical profile denoted increased susceptibility to breast cancer [8].

Comparing the results of this meta-analysis with the previous one published in 2005 [9], it is worth mentioning that the present study seems to have surpassed the limited power of the latter at a certain extent, as we have included nearly a 3-fold larger number of studies. Nevertheless, despite the discrepancies in terms of power, the association between Ala119Ser, Asn453Ser and breast cancer risk remained null, similarly to the initial meta-analysis; the agreement between the two meta-analyses further underlines the validity of the finding. Moreover, in an attempt to inscribe the present meta-analysis into a wider context, it is worth reporting that the most recent meta-analysis on the extensively studied CYP1B1 Val432Leu polymorphism and breast cancer also yielded null results [6]. Taken as a whole, CYP1B1 genotype status does not seem to confer increased risk for breast cancer.

An important secondary message of this meta-analysis is the need for studies on Chinese populations. P450 polymorphisms may well exhibit race-specific effects [1, 12]. As a result, given that the vast majority of data came from Caucasian populations in this meta-analysis, the results may not be safely extrapolated upon Chinese subjects. Similarly, no subanalysis pertaining to menopausal status was feasible, as solely a small subset of studies provided the relevant specific data [9, 32, 35].

Noticeably, an aspect that underlines the validity of the results presented in this meta-analysis is the fact that they persisted after performing a sensitivity analysis. Specifically, after performing the meta-analysis without studies whose genotype frequencies in controls significantly departed from HWE, no substantial modification of the results occurred. The sensitivity analysis has been performed given the fact that deviation from HWE may point to methodological weaknesses, such as biased selection of subjects, genotyping errors or population stratification [17].

In conclusion, this meta-analysis suggests that CYP1B1 Arg48Gly, Ala119Ser and Asn453Ser polymorphisms are not associated with breast cancer risk. Studies on Chinese populations are needed, to elucidate race-specific effects on East Asian populations, if any.

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