Breast Cancer Res Treat (2010) 122:459–469
DOI 10.1007/s10549-009-0694-5

EPIDEMIOLOGY

Four polymorphisms in cytochrome P450 1A1 (CYP1A1) gene and breast cancer risk: a meta-analysis

Theodoros N. Sergentanis · Konstantinos P. Economopoulos

Received: 12 December 2009 / Accepted: 14 December 2009 / Published online: 25 December 2009

Abstract Cytochrome P450s are enzymes which catalyze Phase-I metabolism reactions; cytochrome P450 1A1 (CYP1A1) is a member of the CYP1 family and participates in the metabolism of a vast number of xenobiotics, as well as endogenous substrates. Four single nucleotide polymorphisms in CYP1A1 have been studied concerning their potential implication in terms of breast cancer risk: T3801C, T3205C, A2455G (Ile462Val), and C2453A (Thr461Asp); controversy exists regarding their role. This meta-analysis aims to examine whether the four aforementioned polymorphisms are associated with breast cancer risk. Separate analyses were performed on Caucasian, Chinese, and African populations, as well as on premenopausal and postmenopausal women. Eligible articles were identified by a search of MEDLINE bibliographical database for the period up to October 2009. Concerning T3801C, 32 studies were eligible (11,909 cases and 16,179 controls), 29 studies (12,257 cases and 20,379 controls) were eligible for A2455G, 11 studies (7,189 cases and 8,491 controls) were eligible for C2453A, and eight studies were eligible for T3205C (1,378 cases and 1,642 controls). Pooled odds ratios (OR) were appropriately derived from fixed- or random-effect models. Sensitivity analysis excluding studies whose genotype frequencies in controls significantly deviated from Hardy–Weinberg equilibrium was performed. Homozygous subjects of Caucasian origin carrying the A2455G G allele exhibited elevated breast cancer risk (pooled OR = 2.185, 95% CI 1.253–3.808, fixed effects), whereas heterozygous carriers did not (pooled OR = 1.062, 95% CI 0.852–1.323, random effects). A2455G polymorphism status was not associated with breast cancer risk in Chinese subjects or specifically in premenopausal/postmenopausal women. T3801C, T3205C, and C2453A status were not associated with breast cancer risk at any analysis. In conclusion, this meta-analysis points to the A2455G G allele as a risk factor for breast cancer among Caucasian subjects. On the contrary, T3801C, T3205C, and C2453A status does not seem capable of modifying breast cancer risk.

Keywords CYP1A1 · Cytochrome P450 · A2455G · Polymorphism · Breast cancer

T. N. Sergentanis · K. P. Economopoulos
School of Medicine, National University of Athens, Athens, Greece

T. N. Sergentanis (✉) · K. P. Economopoulos
Society of Junior Doctors, Athens, Greece
e-mail: tsergentanis@sni.gr
URL: www.sni.gr

Introduction

Cytochrome P450s are enzymes that catalyze Phase-I metabolism reactions, such as C-, N- and S-oxidation and dealkylation [1]. Cytochrome P450 1A1 (CYP1A1) is a member of the CYP1 family and participates in the metabolism of a vast number of xenobiotics, as well as endogenous substrates [1]. The metabolism of xenobiotics may well lead to their activation, and in the case of CYP1A1, the activation of benzo[α]pyrene represents a well-studied reaction [1, 2]. Importantly, among endogenous substrates, the involvement of CYP1A1 in the metabolism of estrogen is worth reporting [3].

Four single nucleotide polymorphisms in CYP1A1 have been studied concerning their potential implication in terms of breast cancer risk: T3801C, T3205C and A2455G, C2453A; the two former polymorphisms are located within the 3′-noncoding region, whereas the two latter result in

amino acid substitutions in exon 7 (Ile462Val and Thr461Asp, respectively) [4]. Concerning the biochemical mechanisms underlying the effect of the four polymorphisms, mRNA expression of the gene seems to be the key element, although controversy exists regarding the functional role of each polymorphism [4–6]. Accordingly, attention has been drawn at a meta-analytical level upon the polymorphisms; potential roles of CYP1A1 polymorphisms have been postulated in the context of prostate cancer [7], esophageal cancer [8], oral and pharyngeal cancer [9], and lung cancer [10].

In the context of breast cancer, two meta-analyses have appeared, which have yielded mutually conflicting results. Masson et al. [4] provided a meta-analysis for all four polymorphisms, which demonstrated that none of the four polymorphisms in CYP1A1 gene was associated with breast cancer risk. On the contrary, the meta-analysis by Chen et al. [11] examined two polymorphisms (T3801C and A2455G) in 2007 and suggested that A2455G G/G genotype is associated with increased cancer risk in east-Asians, as well as premenopausal women. Nevertheless, 23 case–control articles have not been included in the most recent meta-analysis examining the association of the above-mentioned CYP1A1 polymorphisms with breast cancer risk; as a result, the need for a recent, up-to-date meta-analysis has become evident.

This meta-analysis aims to examine whether the genotype status of the four polymorphisms in CYP1A1 is associated with breast cancer risk. Separate analyses were performed by race and menopausal status, in an attempt to investigate race-specific and menopausal status-related effects.

Methods

Eligible studies and data abstraction

Eligible articles were identified by a search of MEDLINE bibliographical database for the period up to October 2009 (last search: October 25, 2009) using combinations of the following keywords: "breast," "cancer," "CYP1A1," "cytochrome P-450" or "cytochrome P450", "polymorphism," "T3801C," "A2455G," "T3205C," and "C2453A". 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 analyses were performed in Caucasian (Indo-European), Chinese, and African populations, according to the algorithm adopted in our previous meta-analyses [12–15]. Separate analyses were performed on premenopausal and postmenopausal women. In case of zero cells, an appropriate continuity correction (addition of 0.5) was implemented [12].

The fixed-effect model (Mantel–Haenszel method) or the random-effect (DerSimonian Laird) model was 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 [16]. In case significant heterogeneity was detected, the random-effect model was chosen. Meta-analysis was performed using the "metan" STATA command.

Evidence of publication bias was determined using Egger's [17] 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. The exponentiated coefficient is provided, since the dependent variable in the meta-regression model is log(OR). 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 [18]. For the assessment of the deviation from HWE, the appropriate

goodness-of-fit Chi-square test was performed [18, 19]. 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 91 abstracts retrieved through the search criteria, 39 were irrelevant, eight articles [20–27] were excluded because they were conducted on overlapping populations with other eligible studies [28–35] (these excluded articles represent smaller studies performed on subsets of larger eligible studies), three articles were reviews/meta-analyses [4, 11, 36], and four studies were excluded due to reporting reasons [37–40], i.e., no reporting of the relevant genotype frequencies.

Concerning T3801C polymorphism, 32 studies were eligible (11,909 cases and 16,179 controls) [29, 31–35, 41–63]; 15 studies on Caucasians (6,598 cases and 10,422 controls) [29, 32, 34, 35, 41–44, 48, 49, 51, 56–59]; nine studies on Chinese subjects (2,981 cases and 3,222 controls) [31, 33, 46, 50, 54, 55, 60, 62, 63]; five studies on African subjects (763 cases and 864 controls) [29, 34, 41, 53, 61]; and three on mixed populations (1,567 cases and 1,671 controls) [45, 47, 52].

With respect to A2455G polymorphism, 29 studies were eligible (12,257 cases and 20,379 controls) [28–35, 41, 44, 48–51, 54, 56, 57, 59, 62–69]; 18 studies on Caucasians (9,020 cases and 16,462 controls) [29, 30, 32, 34, 35, 41, 44, 48, 49, 51, 56, 57, 59, 64, 65, 67–69]; eight studies on Chinese subjects (2,881 cases and 3,458 controls) [28, 31, 33, 50, 54, 62, 63, 66]; and three studies on African subjects (356 cases and 459 controls) [29, 34, 41].

With respect to T3205C polymorphism, eight studies were eligible (1,378 cases and 1,642 controls) [29, 34, 41, 53, 61]; three studies on Caucasians (607 cases and 770 controls) [29, 34, 41]; and five studies on African subjects (771 cases and 872 controls) [29, 34, 41, 53, 61]. Concerning the C2453A polymorphism, 11 studies were eligible (7,189 cases and 8,491 controls) [34, 35, 41, 44, 49, 56, 57, 64, 67]; nine studies on Caucasians (6,859 cases and 8,147 controls) [34, 35, 41, 44, 49, 56, 57, 64, 67]; and two studies on African subjects (330 cases and 344 controls) [34, 41].

T3801C polymorphism

The pooled ORs along with their 95% CIs are presented in detail in Table 1. No significant association was demonstrated at any analysis, i.e., overall, race-specific, or menopausal status-related; the same null results persisted in all associations examined, including the dominant and recessive models. The forest plot for heterozygous and homozygous carriers at the overall analysis is depicted in Fig. 1a and b.

Table 1 Pooled ORs by race for heterozygous, homozygous carriers, dominant, and recessive models for the T3801C polymorphism

Race	Heterozygous (TC vs. TT)		Homozygous (CC vs. TT)	
	OR (95% CI)	Test for heterogeneity	OR (95% CI)	Test for heterogeneity
Overall ($n = 32$)	0.984 (0.880–1.100)	$P = 0.002$	0.949 (0.772–1.167)	$P = 0.007$
Caucasian ($n = 15$)	1.041 (0.852–1.273)	$P = 0.008$	0.887 (0.640–1.230)^{F}	$P = 0.352$
Chinese ($n = 9$)	0.973 (0.764–1.239)	$P = 0.006$	0.952 (0.659–1.374)	$P = 0.001$
African ($n = 5$)	0.948 (0.766–1.173)^{F}	$P = 0.285$	1.086 (0.714–1.653)	$P = 0.100$
Premenopausal ($n = 9$)	0.920 (0.788–1.075)^{F}	$P = 0.750$	0.951 (0.742–1.217)^{F}	$P = 0.549$
Postmenopausal ($n = 11$)	0.975 (0.884–1.076)^{F}	$P = 0.762$	1.011 (0.779–1.311)^{F}	$P = 0.185$
Race	Dominant model (CC and TC vs. TT)		Recessive model (CC vs. TT and TC)	
	OR (95% CI)	Test for heterogeneity	OR (95% CI)	Test for heterogeneity
Overall ($n = 32$)	0.993 (0.896–1.100)	$P < 0.001$	0.948 (0.797–1.128)	$P = 0.038$
Caucasian ($n = 15$)	1.058 (0.908–1.233)	$P = 0.005$	0.891 (0.645–1.231)^{F}	$P = 0.461$
Chinese ($n = 9$)	0.998 (0.786–1.268)	$P < 0.001$	0.957 (0.715–1.280)	$P = 0.003$
African ($n = 5$)	0.960 (0.784–1.176)	$P = 0.124$	1.097 (0.727–1.655)	$P = 0.203$
Premenopausal ($n = 9$)	0.969 (0.777–1.208)	$P = 0.084$	0.989 (0.785–1.246)^{F}	$P = 0.534$
Postmenopausal ($n = 11$)	0.997 (0.912–1.089)^{F}	$P = 0.101$	1.041 (0.812–1.334)^{F}	$P = 0.128$

All pooled ORs were derived from random-effect models except for cells marked with (fixed^{F})

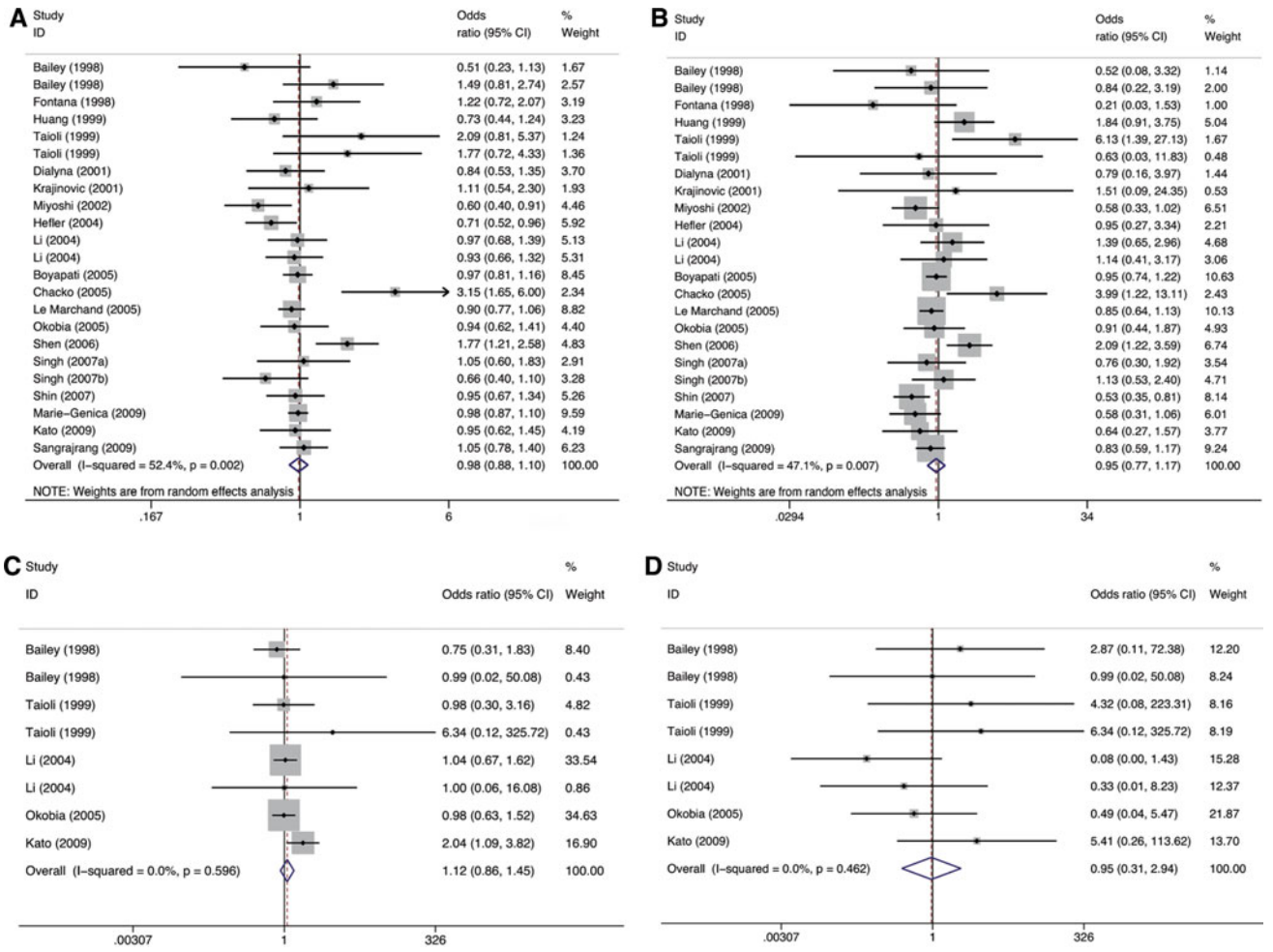

Fig. 1 Forest plot for the overall association between T3801C polymorphism and breast cancer risk for **a** heterozygous and **b** homozygous carriers (random effects). Forest plot for the overall association between T3205C polymorphism and breast cancer risk for **c** heterozygous and **d** homozygous carriers (fixed effects). 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*)

Concerning the overall analysis, publication bias was not detected at any comparison ($P = 0.383$ for the analysis on heterozygous carriers, $P = 0.470$ for the analysis on homozygous carriers, $P = 0.190$ for the dominant model, $P = 0.458$ for the recessive model). The same results were yielded when the analysis was stratified by race (data not shown).

Meta-regression with publication year did not point to any significant modifying role upon the effect of T3801C, either at the TC versus TT comparison ($P = 0.986$), CC versus TT comparison ($P = 0.262$), or the dominant model ($P = 0.970$); at the recessive model a borderline effect was detected (exponentiated coefficient: 0.944, 95% CI 0.890–1.001, $P = 0.055$). When the analysis was stratified by race, no significant associations were detected (data not shown).

Examining genotype frequencies in controls, significant deviation from HWE was detected in four studies, i.e., the Caucasian part of the study by Bailey et al. [41], the Caucasian part of the study by Taioli et al. [29], the study by Chacko et al. [51] and Shin et al. [63]. After the exclusion of the four studies significantly departing from HWE the results remained practically unchanged. Specifically, at the overall analysis the pooled ORs were as follows: 0.938 (0.848–1.037, random effects) for heterozygous carriers, 0.963 (0.789–1.176, random effects) for homozygous carriers, 0.959 (0.872–1.056, random effects) for the dominant model, and 0.951 (0.844–1.072, fixed effects) for the recessive model. Accordingly, the race-specific results presented in Table 1 remained practically unchanged, as once again no associations reached significance (data not shown for reasons of brevity).

It is worth mentioning that in nine studies [32, 45–47, 49, 54, 58–60], however, the deviation from HWE could not be assessed due to reporting reasons, i.e., categories of genotypes merged in the individual studies.

T3205C polymorphism

The pooled ORs along with their 95% CIs are presented in detail in Table 2. No significant associations were demonstrated at any analysis, i.e., overall, race-specific, or menopausal status-related. The forest plot for heterozygous and homozygous carriers at the overall analysis is depicted in Fig. 1c and d.

Concerning the overall analysis, publication bias was not detected at any comparison ($P = 0.698$ for the analysis on heterozygous carriers, $P = 0.191$ for the analysis on homozygous carriers, $P = 0.784$ for the dominant model, $P = 0.188$ for the recessive model). The same results were yielded when the analysis was stratified by race (data not shown).

Meta-regression with publication year did not point to any significant modifying role upon the effect of T3205C, either at the TC versus TT comparison ($P = 0.143$) CC versus TT comparison ($P = 0.620$), the dominant model ($p = 0.131$) or at the recessive model ($P = 0.586$). The same results were yielded when the analysis was stratified by race (data not shown).

Examining genotype frequencies in controls, significant deviation from HWE was detected in one study, i.e., the Caucasian part of the study by Li et al. [34]. After the exclusion of this study, the results remained practically unchanged, as the associations still did not reach significance. Specifically, at the overall analysis the pooled ORs were as follows: 1.118 (0.863–1.448, fixed effects) for heterozygous carriers, 1.106 (0.332–3.687, fixed effects) for homozygous carriers, 1.083 (0.839–1.398, fixed effects) for the dominant model, and 1.101 (0.331-3.665, fixed effects) for the recessive model. Accordingly, the race-specific results remained practically unchanged (data not shown for reasons of brevity).

A2455G polymorphism (Ile462Val)

The pooled ORs along with their 95% CIs are presented in Table 3. In Caucasian populations, homozygous carriers exhibited elevated breast cancer risk; accordingly, the recessive model yielded statistically significant results. No significant association was demonstrated, at the overall analysis, at the race-specific analyses pertaining to Chinese and African subjects or at the subanalyses performed on pre- and postmenopausal women. The forest plot for heterozygous and homozygous carriers at the overall analysis is depicted in Fig. 2a and b; the statistically significant results pertaining to Caucasian subjects appear in Fig. 2c and d.

Regarding the overall analysis, publication bias was detected at the analysis on homozygous carriers ($P = 0.052$) and at the recessive model ($P = 0.058$); on the contrary, no publication bias became evident at the analysis on heterozygous carriers ($P = 0.440$) or at the dominant model ($P = 0.255$). No significant publication bias was detected however at either subanalysis pertaining to Caucasian or Chinese populations, probably due to the limited power of the formal statistical tests.

Meta-regression with publication year did not point to any significant modifying role upon the effect of A2455G either at the AG versus AA comparison ($P = 0.816$), GG versus AA comparison ($P = 0.726$), the dominant model ($P = 0.687$); or at the recessive model ($P = 0.717$).

Table 2 Pooled ORs by race for heterozygous, homozygous carriers, dominant, and recessive models for the T3205C polymorphism

Race	Heterozygous (TC vs. TT)		Homozygous (CC vs. TT)	
	OR (95% CI)	Test for heterogeneity	OR (95% CI)	Test for heterogeneity
Overall ($n = 8$)	1.117 (0.863–1.445)	$P = 0.596$	0.954 (0.309–2.944)	$P = 0.462$
Caucasian ($n = 3$)	1.580 (0.222–11.267)	$P = 0.727$	1.052 (0.129–8.590)	$P = 0.524$
African ($n = 5$)	1.110 (0.856–1.440)	$P = 0.312$	0.917 (0.241–3.486)	$P = 0.250$
Premenopausal ($n = 3$)	0.848 (0.609–1.181)	$P = 0.740$	0.848 (0.200–3.604)	$P = 0.244$
*P*ostmenopausal ($n = 3$)	1.371 (0.990–1.898)	$P = 0.150$	0.247 (0.039–1.585)	$P = 0.668$
Race	Dominant model (CC and TC vs. TT)		Recessive model (CC vs. TT and TC)	
	OR (95% CI)	Test for heterogeneity	OR (95% CI)	Test for heterogeneity
Overall ($n = 8$)	1.074 (0.833–1.384)	$P = 0.413$	0.950 (0.308–2.929)	$P = 0.467$
Caucasian ($n = 3$)	0.996 (0.162–6.140)	$P = 0.559$	1.052 (0.129–8.589)	$P = 0.524$
African ($n = 5$)	1.076 (0.833–1.389)	$P = 0.200$	0.911 (0.240–3.461)	$P = 0.255$
Premenopausal ($n = 3$)	0.838 (0.606–1.160)	$P = 0.455$	0.873 (0.206–3.704)	$P = 0.248$
*P*ostmenopausal ($n = 3$)	1.269 (0.921–1.747)	$P = 0.102$	0.235 (0.037–1.509)	$P = 0.696$

All pooled ORs have been derived from fixed-effects models

Table 3 Pooled ORs by race for heterozygous, homozygous carriers, dominant, and recessive models for the A2455G (Ile462Val) polymorphism

Race	Heterozygous (AG vs. AA)		Homozygous (GG vs. AA)	
	OR (95% CI)	Test for heterogeneity	OR (95% CI)	Test for heterogeneity
Overall ($n = 29$)	1.044 (0.914–1.193)	$P = 0.001$	1.137 (0.837–1.543)	$P = 0.095$
Caucasian ($n = 18$)	1.062 (0.852–1.323)	$P < 0.001$	**2.185 (1.253–3.808)**^{F}	$P = 0.161$
Chinese ($n = 8$)	0.997 (0.892–1.115)^{F}	$P = 0.293$	0.873 (0.700–1.089)^{F}	$P = 0.578$
African ($n = 3$)	1.322 (0.637–2.743)^{F}	$P = 0.778$	1.689 (0.174–16.378)^{F}	$P = 0.837$
Premenopausal ($n = 7$)	0.938 (0.748–1.176)^{F}	$P = 0.857$	0.663 (0.375–1.172)^{F}	$P = 0.115$
Postmenopausal ($n = 11$)	1.084 (0.849–1.385)	$P = 0.035$	0.951 (0.639–1.416)^{F}	$P = 0.241$
Race	Dominant model (GG and AG vs. AA)		Recessive model (GG vs. AA and AG)	
	OR (95% CI)	Test for heterogeneity	OR (95% CI)	Test for heterogeneity
Overall ($n = 29$)	1.058 (0.929–1.204)	$P < 0.001$	0.984 (0.807–1.201)^{F}	$P = 0.176$
Caucasian ($n = 18$)	1.115 (0.911–1.366)	$P < 0.001$	**2.076 (1.193–3.614)**^{F}	$P = 0.247$
Chinese ($n = 8$)	0.952 (0.860–1.055)^{F}	$P = 0.222$	0.876 (0.708–1.086)^{F}	$P = 0.617$
African ($n = 3$)	1.322 (0.637–2.743)^{F}	$P = 0.778$	1.658 (0.171–16.068)^{F}	$P = 0.841$
Premenopausal ($n = 7$)	0.984 (0.800–1.212)^{F}	$P = 0.127$	0.680 (0.222–2.085)	$P = 0.092$
Postmenopausal ($n = 11$)	1.187 (0.941–1.497)	$P = 0.002$	0.920 (0.622–1.362)^{F}	$P = 0.383$

All pooled ORs were derived from random-effects models except for cells marked with (fixed^{F})

Bold values denote statistical significance

Similarly, when the analysis was stratified by race, no significant associations were detected (data not shown).

Examining genotype frequencies in controls, significant deviation from HWE was detected in two studies [48, 69], which were both performed on Caucasian subjects. After the exclusion of the two studies significantly departing from HWE the associations demonstrated in Caucasian populations retained their statistical significance. Specifically, the pooled ORs pertaining to Caucasians were as follows: 0.986 (0.796–1.220, random effects) for heterozygous carriers, 2.317 (1.290–4.160, fixed effects) for homozygous carriers, 1.068 (0.869–1.313, random effects) for the dominant model, and 2.221 (1.239–3.982, fixed effects) for the recessive model. Worthy of note, however, the deviation from HWE could not be assessed due to reporting reasons in five studies [32, 49, 54, 59, 65].

C2453A polymorphism (Thr461Asp)

The pooled ORs along with their 95% CIs are presented in Table 4; no significant associations were demonstrated. No race-specific subanalyses were attempted, as all studies except for solely two pertained to Caucasian populations. The forest plot for heterozygous and homozygous carriers at the overall analysis is depicted in Fig. 3a and b.

Concerning the overall analysis, publication bias was not detected at any comparison ($P = 0.455$ for the analysis on heterozygous carriers, $P = 0.706$ for the analysis on homozygous carriers, $P = 0.287$ for the dominant model, $P = 0.723$ for the recessive model).

Meta-regression with publication year did not point to any significant modifying role upon the effect of C2453A, either at the CA versus CC comparison (exponentiated coefficient: 0.987, 95% CI 0.947–1.030, $P = 0.510$), AA versus CC comparison ($P = 0.782$), the dominant model ($P = 0.627$); or at the recessive model ($P = 0.760$).

Examining genotype frequencies in controls, significant deviation from HWE was detected in one study [57]. After the exclusion of this study, the results remained practically unchanged, as the associations still did not reach significance. Specifically, at the overall analysis the pooled ORs were as follows: 0.987 (0.869–1.122, fixed effects) for heterozygous carriers, 1.376 (0.735–2.573, fixed effects) for homozygous carriers, 0.987 (0.873–1.115, fixed effects) for the dominant model, and 1.362 (0.728–2.547, fixed effects) for the recessive model.

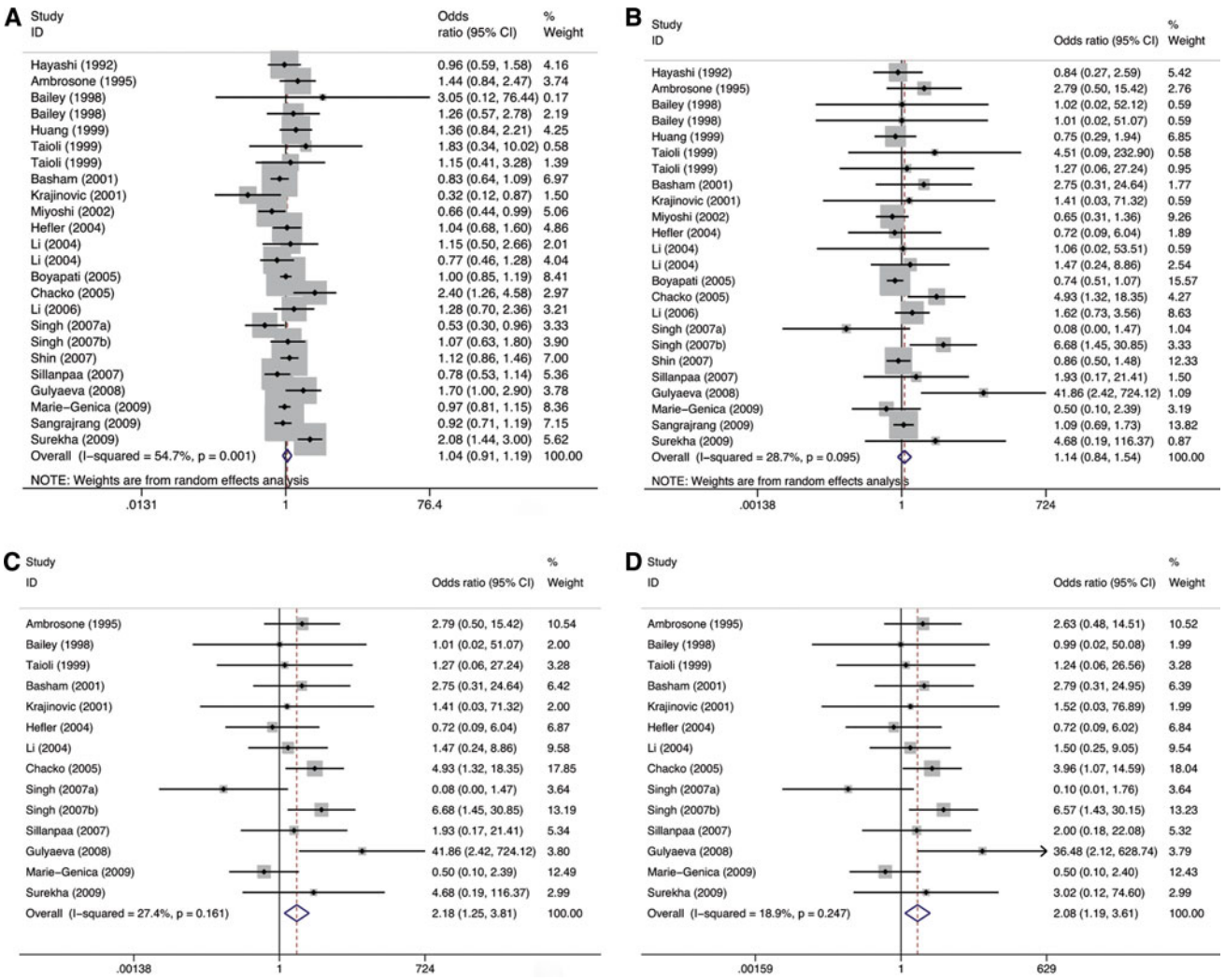

Fig. 2 Forest plot for the overall association between A2455G polymorphism and breast cancer risk for **a** heterozygous and **b** homozygous carriers (random effects). Forest plot for the association between A2455G polymorphism and breast cancer risk for Caucasian subjects **c** for homozygous carriers and **d** following a recessive model (fixed effects)

Table 4 Pooled ORs by race for heterozygous, homozygous carriers, dominant, and recessive models for the C2453A (Thr461Asp) polymorphism

Race	Heterozygous (AC vs. CC)		Homozygous (AA vs. CC)	
	OR (95% CI)	Test for heterogeneity	OR (95% CI)	Test for heterogeneity
Overall ($n = 11$)	0.985 (0.868–1.117)	$P = 0.824$	1.546 (0.862–2.722)	$P = 0.923$
Premenopausal ($n = 5$)	1.020 (0.638–1.630)	$P = 0.263$	2.709 (0.560–13.107)	$P = 0.793$
Postmenopausal ($n = 6$)	0.931 (0.797–1.088)	$P = 0.305$	1.641 (0.781–3.450)	$P = 0.518$
Race	Dominant model (AA and AC vs. CC)		Recessive model (AA vs. CC and AC)	
	OR (95% CI)	Test for heterogeneity	OR (95% CI)	Test for heterogeneity
Overall ($n = 11$)	0.992 (0.880–1.120)	$P = 0.822$	1.535 (0.856–2.751)	$P = 0.929$
Premenopausal ($n = 5$)	0.944 (0.633–1.410)	$P = 0.510$	2.796 (0.580–13.482)	$P = 0.793$
Postmenopausal ($n = 6$)	1.090 (0.769–1.544)^{R}	$P = 0.092$	1.633 (0.777–3.432)	$P = 0.541$

All pooled ORs were derived from fixed-effect models except for cells marked with (random^{R})

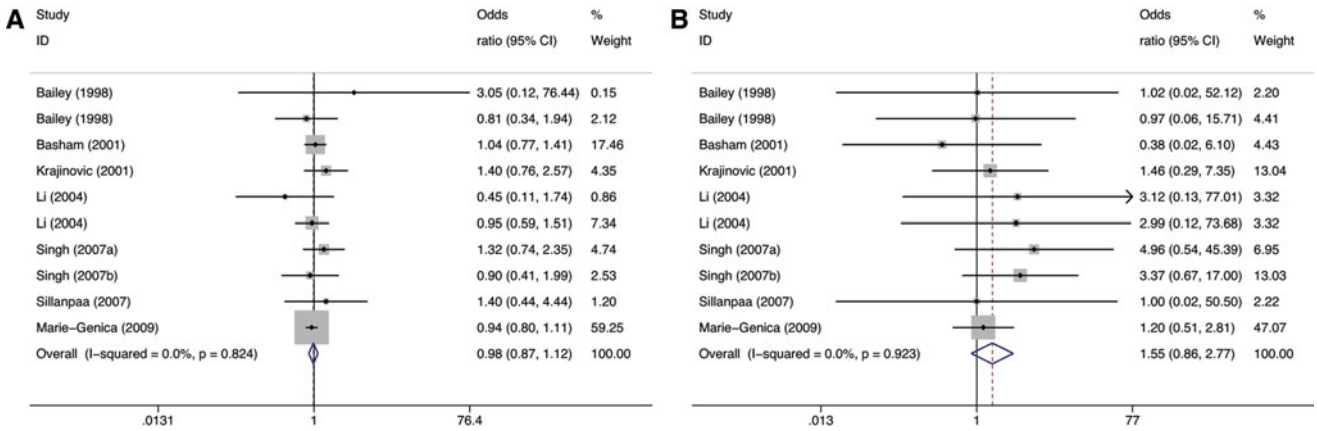

Fig. 3 Forest plot for the overall association between C2453A polymorphism and breast cancer risk for **a** heterozygous and **b** homozygous carriers (fixed effects)

Discussion

The principal message of this meta-analysis is the positive association between the A2455G (Ile462Val) G allele and increased risk for breast cancer among Caucasian subjects. The association followed a recessive pattern, as homozygous (GG) carriers seemed to be at particular risk; on the other hand, heterozygous carriers of Caucasian origin did not present with elevated breast cancer risk. Worthy of note, T3801C, T3205C, and C2453A status were not associated with breast cancer risk.

Comparing the results of this meta-analysis with previous ones, it is worth mentioning that this meta-analysis surpasses the limited power (due to the limited number of studies) of the first meta-analysis on the field [4] and seems thus capable of documenting a positive association in the context of A2455G, while it confirms the null associations concerning the remaining three polymorphisms.

Nevertheless, when comparing the results of the present meta-analysis with that by Chen et al. [11] published 2 years ago, a marked discrepancy emerges and seems worth commenting. Contrary to our meta-analysis, Chen et al. demonstrated that the association implicating the A2455G G allele pertained to East Asian populations and premenopausal women. Regarding the issue of race, close inspection of data revealed that during the examination of "East Asian" populations, Chen et al. had merged a study on Indian populations [56] with other studies on Chinese and Japanese subjects; in our algorithm [12–15], Indian studies have been included in the greater subset of Caucasian (Indo-european) race, a fact which seems closer to the existing data in the field of physical anthropology [70]. Importantly, it should be declared that merging of Chinese/Japanese and Indian studies given the larger sample of studies in the present meta-analysis still did not lead to significant results (data not shown).

With respect to menopausal status, the present meta-analysis does not confirm the association that Chen et al. [11] supported, i.e., A2455G status seems capable of modifying breast cancer risk in premenopausal women. In the wider set of studies included in our meta-analysis, no associations became evident either for premenopausal or for postmenopausal women. It is worth reporting that the results of this meta-analysis pertaining to A2455G are based on seven case–control studies on premenopausal women and eleven on postmenopausal ones; on the contrary, the meta-analysis by Chen et al. [11] had included solely four and five studies, respectively.

Noticeably, an aspect that points to the validity of the results presented in this meta-analysis is the fact that they persisted after performing a sensitivity analysis. Specifically, performing the meta-analysis without studies whose genotype frequencies in controls significantly departed from HWE, did not result in any substantial modification of the results. The sensitivity analysis has been performed under the light of fact that deviation from HWE may point to methodological weaknesses, such as biased selection of subjects, genotyping errors, or population stratification [18].

In conclusion, this meta-analysis points to the A2455G (Ile462Val) G allele as a risk factor for breast cancer among Caucasian subjects. On the contrary, T3801C, T3205C, and C2453A status does not seem capable of modifying breast cancer risk.

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