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Research article

Associations of *CYP1A1* gene polymorphisms and risk of breast cancer in Indian women: a meta-analysis

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Abstract: Reported associations of *CYP1A1* polymorphisms with breast cancer have been inconsistent. In this meta-analysis examining breast cancer associations of three *CYP1A1* polymorphisms (M1, M2 and M4) among Indian women may yield information that may be of clinical and epidemiological use for this particular demography. We searched MEDLINE using PubMed and Embase for association studies. From seven published case-control studies, we estimated overall associations and applied subgroup analysis to explore differential effects. All three polymorphisms exhibited overall increased risk, significant in M1 (OR 1.61–1.65, $p = 0.04$) and M4 (OR 2.02–3.92, $p = 0.02$–0.04). Differential effects were observed only in the M1 polymorphism where M1 effects were significant in South Indians (OR 2.20–4.34, $p < 0.0001$) but not the North population, who were at reduced risk (OR 0.64–0.77, $p = 0.03$–0.55). These populations were not materially different in regard to M2 and M4 as did the women stratified by menopausal status. In this meta-analysis, M1 and M4 effects may render Indian women susceptible, but may be limited by heterogeneity of the studies. Differential effects of the M1 polymorphism in breast cancer render South Indians susceptible compared to those in the North.

Keywords: breast cancer; *CYP1A1*; meta-analysis; polymorphisms

1. Introduction

Breast cancer is a leading cause of death among women in India [1]. The multifactorial nature of this disease is marked by the synergy of interaction among various environmental and genetic factors [2,3]. One genetic factor is the *CYP1A1* protein, encoded by CYP1A1 gene, an interesting candidate that might influence susceptibility to breast cancer risk for reasons mentioned by Chen et al. [4]. *CYP1A1* gene polymorphisms have been extensively studied, especially in relation to breast cancer susceptibility [4-13]. The *CYP1A1* gene, located at 15q22–q24, comprises seven exons and six introns spanning 5810 base pairs [14]. Of the four common polymorphisms of the *CYP1A1* gene identified, we examine three in the Indian population: M1 (rs4646903: T3801C, giving rise to a *MspI* restriction site in the 3'-noncoding region [15], M2 (rs1048943: A2455G), resulting in an amino acid change at codon 462 from isoleucine to valine within the heme-binding domain of exon 7 [16]; and M4 (rs1799814: C2453A), resulting in an amino acid substitution of threonine with asparagine at codon 461 [17]. Of the three polymorphisms, M4 is very rare.

Though the functional significance of variant *CYP1A1* genotypes is unclear [4], studies of CYP1A1 in cultured human lymphocytes showed significantly elevated levels of inducible enzyme activity among M2 genotypes compared with the wild-type genotype [18]. M2 alleles appear to be associated with *CYP1A1* inducibility at the level of transcription followed by 3-fold elevation in aryl hydrocarbon hydroxylase enzyme activity [19]. The M1 allele was also reported to be more readily inducible than the *CYP1A1* wild-type allele [20,21]. A number of meta-analyses have appeared addressing associations of *CYP1A1* polymorphisms with breast cancer. To our knowledge, no meta-analysis, including the four we chose to compare our study with, has focused on a population of a single country in Asia. Yet three of them examined *CYP1A1* associations with breast cancer in Asian populations using subgroup analysis. Yao et al. [6] and Chen et al. [4] did this among Asians in general and east-Asians, respectively. Still these populations were a heterogeneous mix of different Asian nationalities. The Sergentanis et al. [5] examination of the Chinese population was more homogeneous. Still none of these meta-analyses have addressed *CYP1A1* associations with breast cancer in the Indian population. Given that breast cancer is an overriding epidemiological issue in India [9] and that reports do not necessarily agree with each other, we conducted a meta-analysis of published case-control studies to examine the effect of *CYP1A1* genetic polymorphisms on breast cancer risk among Indian women.

2. Materials and Method

2.1. Selection of studies

Two strategies were used in searching MEDLINE using PubMed and Embase. In the first, search terms were broad such as "*DNA polymorphism*", "*breast cancer*" and "*xenobiotic*". In a separate second search, search terms were more specific: "*CYP1A1*" and "*cytochrome P450 1A1*". The broad and specific search terms were combined with "*breast cancer*" and "*Indian*" to find association studies as of 14 April 2015. Studies were eligible if they had genotypic data with a case-control design

restricted to English. Figure 1 outlines our study selection process in a flowchart following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [22]. The two search strategies yielded a total of 31 citations, 23 of which were screened for not fulfilling our inclusion criteria. Excluding a duplicate article, full texts of the remaining seven were obtained which were judged as eligible; as such, they were included in the meta-analysis. We manually searched the reference sections of each of these studies for additional articles. Syamala et al. [7] provided sporadic and familial data thus were treated as separate studies. In all, this meta-analysis had a total number of eight studies from seven publications [7-13].

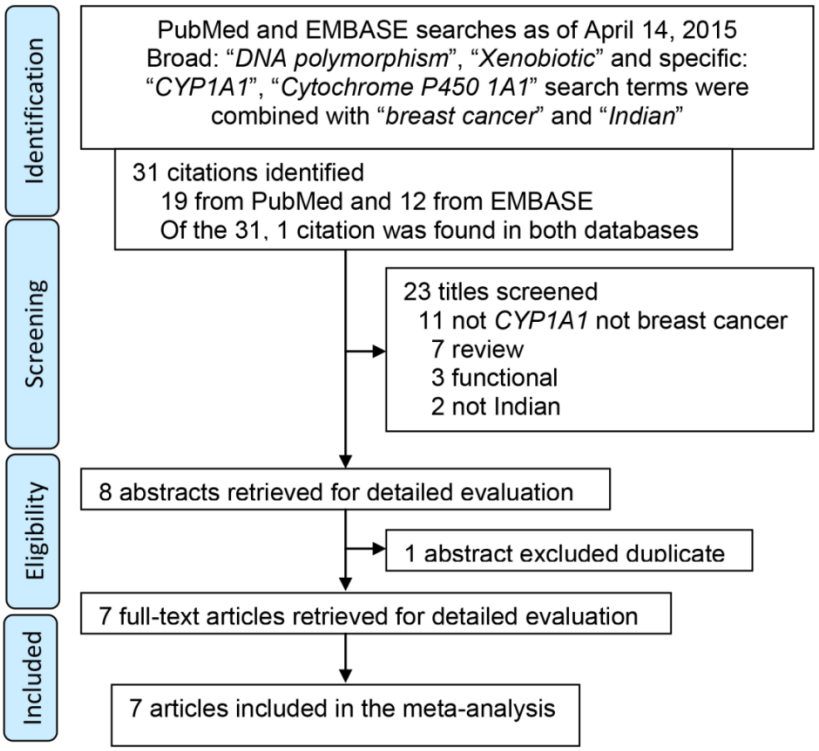

Figure 1. Flowchart of literature search and selection.

2.2. Data extraction

Two investigators independently extracted data and reached consensus on all the items. The following information was obtained from each publication: first author's name, published year, city and region in India, state of controls, matching criteria, sample source, genotype data, number of cases and controls. We also calculated frequencies of the variant allele as well as deviations of the controls from the Hardy-Weinberg equilibrium (HWE).

2.3. Quality assessment of the studies

Quality of the studies was evaluated with use of the Newcastle–Ottawa Scale (NOS) [23]. Each study was assessed based on three broad perspectives: selection, comparability, and exposure with a score ranging from 0 to 9. Study quality scores for high, medium and poor were ≥ 7, 4–6 and < 4, respectively.

2.4. Meta-analysis

Risks (odds ratios [ORs] and 95% confidence intervals) of breast cancer in three *CYP1A1* polymorphisms (M1, M2, and M4) were estimated for each study. Pooled ORs were calculated for the following genetic models using variant (*var*) and wild-type (*wt*) genotypes: (i) homozygous (*var-var*, genotypes compared with the *wt-wt*), (ii) recessive (*var-var* vs. *wt-var* + *wt-wt*) (iii) dominant (*var-var* + *wt-var* vs. *wt-wt*) and (iv) co-dominant genetic model (*var* vs. *wt*)**.** To compare effects on the same baseline, we used raw data for genotype frequencies to calculate study-specific estimates of the OR. Pooled ORs were obtained using either the fixed [24] (in absence of heterogeneity) or random [25] (in its presence) effects models. Heterogeneity between studies was estimated using the I^2-based Q test [26] and quantified with the I^2 statistic which measures degree of inconsistency among studies [27]. Given the low power of the heterogeneity test [28], significance threshold was set at $p = 0.10$. Sources of heterogeneity were examined with subgroup analysis [27]. Sensitivity analysis, which involved omitting one study at a time and recalculating the pooled OR, was also used to test for robustness of the summary effects. Availability of analyzable data from the South and North Indian subpopulations from the included studies allowed this type of geographical subgrouping. Supported by precedent literature [29,30], the probability of differential risk associations between the South and North Indian subpopulations warranted testing for the presence of interactions; wherein the generated p values were subjected to the Bonferroni correction. Data were analyzed using Review Manager 5.3 (Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration, 2014) and SigmaStat 3.5 (Systat Software, San Jose, CA). Significance was set at a *p*-value of ≤ 0.05 throughout except in heterogeneity estimation. Publication bias was not investigated because of the low sensitivity of the qualitative and quantitative tests when the number of studies is lower than ten [31].

3. Results

3.1. Study characteristics

Table 1 shows features of the included studies, published between 2005 and 2011. Five studies had Southern subjects [7,8,11-13] compared to two from the North [9,10]. There were more hospital-based [7,10-12] than population-based [8,9,13] studies. Two studies made no mention of matching [11,13]. Methodological quality of the studies indicates that they were moderate with most studies having a score of 6–7.

Table S1 summarizes genotypic features of the component studies in the meta-analysis. In the M1 polymorphism association studies (1151 cases/1527 controls), populations of South and North India were examined in four [7,11-13] and two [9,10] papers, respectively. These Indian geographical regions were likewise examined in four [8-11] and two [12,13] papers on the M2 polymorphism (1039 cases/1022 controls). The two studies [9,10] and a single one [11] on the M4 polymorphism (631 cases/611 controls) had North and South Indian subjects, respectively. Control subjects deviated from the HWE in the following: (i) two studies [9,12] in M1; and (ii) one study for M2 [8] and two for M4 [10,11]. For both M1 and M2, the mean frequency of the minor allele was greater from the Northern populations, though this was significant only for M1 (M1: North $\bar{x} = 0.32 \pm 0.08$ standard deviation (SD) versus South $\bar{x} = 0.18 \pm 0.05$ SD, $p = 0.03$; M2: North $\bar{x} = 0.18 \pm 0.06$ SD versus South $\bar{x} = 0.16 \pm 0.11$ SD, $p = 0.81$).

Table 1. Characteristics of the included studies that examine associations of the *CYP1A1* polymorphisms with breast cancer among Indian women.

First author	Year	Indian city	Indian region	State of controls	Source of controls	Matching criteria	NOS
Singh N	2007	Lucknow	North	normal	Hospital	menopause, diet	6
Singh V	2007	Lucknow	North	healthy	Population	residence	7
Surekha	2009	Hyderabad	South	healthy	Population	age	7
Chacko	2005	Kerala	South	healthy	Hospital	age, menopause	6
Syamala*	2010	Thiruvanan	South	cancer-free	Hospital	residence, gender	6
Naushad	2011	Hyderabad	South	healthy	Hospital	no mention	4
Kiruthiga	2011	Madurai	South	no mention	Population	no mention	5

* Separate familial and sporadic data were considered as two studies; NOS: Newcastle-Ottawa Score.

Table S2 shows genotypic frequencies in the three *CYP1A1* polymorphisms in premenopausal (M1: 279 cases/309 controls; M2: 277 cases/309 controls) and postmenopausal (M1: 230 cases/251 controls; M2: 232 cases/251 controls) women. The M1 and M2 polymorphisms had three studies each [9,10,12]. In the M4 polymorphism, premenopausal (168 cases/197 controls) and postmenopausal (118 cases/139 controls) subjects were all North Indians on account of two studies [9,10], one of which deviated from the HWE [10]. In the geography and menopausal status analyses, the probability of differential risk associations between North and South India as well as premenopausal and postmenopausal women warranted testing for presence of interactions.

3.2. Overall findings

In Table 2, all three polymorphisms showed overall increased risk across all comparisons. Significance was observed in the M1 (OR 1.61–3.43, p = 0.007–0.04) and M4 (OR 2.02–3.92, p = 0.02–0.04) polymorphisms. The significant homozygous and recessive M4 effects (OR 3.81–3.92, p = 0.02) were obtained in the absence of heterogeneity ($p_{\text{heterogeneity}}$ = 0.79–0.84, I^2 = 0%). All other effects in all the polymorphisms were heterogeneous, particularly high for M1 ($p_{\text{heterogeneity}}$ < 0.00001, I^2 = 85–96%). Figure 2 exemplifies the significant effects of M1 under conditions of high heterogeneity.

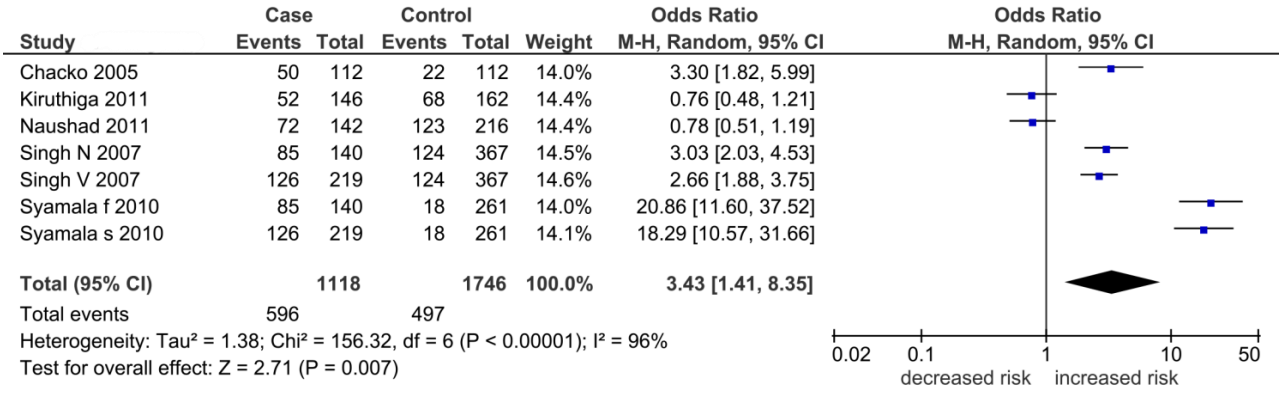

Figure. 2 Forest plot of association of the CYP1A1 M1 polymorphism on breast cancer in the overall analysis in the dominant genetic model of the overall analysis.

Diamond denotes the pooled odds ratio (OR). Squares indicate the OR in each study, with square sizes directly proportional to the weight contribution (%) of each study. Horizontal lines represent 95% confidence intervals (CI). The Z test for overall effect indicates significance if $p < 0.05$. The chi-square test indicates heterogeneity ($p < 0.10$) warranting use of the random-effects model.

Table 2. Summary OR associations of all *CYP1A1* polymorphisms with breast cancer among Indian women.

		Test of association				Test of heterogeneity	
	Genetic model	N	OR	95% CI	p^A	p^B	I^2 (%)
M1	Homozygous	7	2.31	0.98–5.46	0.06	<0.0001	88
	Recessive	7	2.02	0.95–4.29	0.07	<0.0001	85
	Dominant	7	**3.43**	**1.41–8.35**	**0.007**	<0.0001	96
	Codominant	7	**1.61**	**1.03–2.52**	**0.04**	<0.0001	92
M2	Homozygous	6	2.53	0.65–9.95	0.18	0.003	72
	Recessive	6	2.39	0.68–8.42	0.18	0.009	68
	Dominant	6	1.50	0.83–2.74	0.18	<0.0001	89
	Codominant	6	1.51	0.89–2.58	0.13	<0.0001	90
M4	Homozygous	2	**3.92**	**1.25–12.33**	**0.02**	0.79	0
	Recessive	2	**3.81**	**1.22–11.96**	**0.02**	0.84	0
	Dominant	2	1.96	0.87–4.43	0.11	0.003	83
	Codominant	2	**2.02**	**1.03–3.95**	**0.04**	0.01	78

N: number of studies; OR: odds ratio; CI: confidence interval; p^A and p^B: p values for association and heterogeneity with significance set at < 0.05 and < 0.10, respectively; Values in **bold** indicate significant tests of association; R: Random-effects model; F: Fixed-effects model.

3.3. Subgroup analysis

3.3.1. Geography

Table 3 shows subgroup associations stratified by geography in the M1 polymorphism. Mainly, the North Indians were protected (OR 0.64–0.77, $p = 0.03$–0.55), but not their Southern counterparts, who were at significant risk (OR 2.20–4.34, $p < 0.0001$). The tests of interaction highlight these contrasting effects, with significance generated in all ($p = 0.00002$–0.02) but the recessive model. Table 4 compares increased risk effects between the two Indian populations in the M2 polymorphism which did not materially differ given the non-significance of the p values of interaction ($p > 1$).

3.3.2. Menopausal subgroup

In all three polymorphisms, differential effects between premenopausal and postmenopausal women were not significant (Tests for Interaction: $p > 1$) where both subgroups generally exhibited increased risk effects (Tables 3–4). These effects were significant in the codominant model of M2 and M4 among postmenopausal women (Tables 4 and 5), suggesting this subgroup to be at particular risk.

Among premenopausal women, M2 effects indicated codominant null and protective dominant effects suggesting variability of the results (Table 4).

Table 3. Subgroup associations of the M1 *CYP1A1* polymorphisms with breast cancer among Indian women.

	South India					North India					
	n = 5					*n* = 2					
	Test of association			Test of heterogeneity		Test of association			Test of heterogeneity		
	OR	95% CI	p^A	p^B	I^2	OR	95% CI	p^A	p^B	I^2	*p*i
Homozygous	**4.34**	**3.07–6.12**	**<0.0001**	0.20	33	0.64	0.22–1.93	0.43	0.03	78	**0.019**
Recessive	**3.55**	**2.54–4.95**	**<0.0001**	0.50	0	0.69	0.20–2.34	0.55	0.01	83	0.23
Dominant	**3.73**	**0.88–15.71**	**0.007**	<0.0001	97	**2.81**	**2.16–3.65**	**<0.0001**	0.63	0	>1
Codominant	**1.17**	**1.00–1.37**	**0.05**	<0.0001	86	**2.72**	**2.23–3.31**	**<0.0001**	0.65	0	>1
	Premenopausal					Postmenopausal					
	n = 3					*n* = 3					
	Test of association			Test of heterogeneity		Test of association			Test of heterogeneity		
	OR	95% CI	p^A	p^B	I^2	OR	95% CI	p^A	p^B	I^2	*p*i
Homozygous	1.87	0.63–5.53	0.26	0.04	68	1.35	0.53–3.41	0.53	0.09	58	>1
Recessive	1.67	0.65–4.30	0.29	0.07	62	1.54	0.92–2.60	0.10	0.19	40	>1
Dominant	1.30	0.92–1.81	0.13	0.23	31	1.03	0.56–1.86	0.94	0.09	58	>1
Codominant	1.31	0.87–1.97	0.20	0.08	60	1.08	0.67–1.75	0.74	0.06	65	>1

OR: odds ratio; CI: confidence interval; p^A and p^B: *p* values for association and heterogeneity with significance set at < 0.05 and < 0.10, respectively; p_i: *p* values for tests of interaction after Bonferroni correction; Values in **bold** are significant in the tests of association and tests of interaction

Table 4. Subgroup OR associations of the M2 *CYP1A1* polymorphisms with breast cancer among Indian women.

	South India					North India					
	n = 5					*n* = 2					
	Test of association			Test of heterogeneity		Test of association			Test of heterogeneity		
	OR	95% CI	p^A	p^B	I^2	OR	95% CI	p^A	p^B	I^2	*p*i
Homozygous	3.72	0.55–25.44	0.18	0.006	81	1.36	0.06–31.06	0.85	0.009	79	>1
Recessive	3.34	0.60–18.59	0.17	0.02	76	1.26	0.06–24.67	0.88	0.01	77	>1
Dominant	2.37	0.63–8.92	0.20	<0.0001	92	1.17	0.54–2.55	0.69	<0.0001	89	>1
Codominant	2.81	0.75–10.51	0.12	<0.0001	94	1.10	0.58–2.09	0.76	0.0001	89	>1
	Premenopausal					Postmenopausal					
	n = 3					*n* = 3					
	Test of association			Test of heterogeneity		Test of association			Test of heterogeneity		
	OR	95% CI	p^A	p^B	I^2	OR	95% CI	p^A	p^B	I^2	*p*i
Homozygous	1.69	0.20–14.35	0.63	0.03	73	1.79	0.89–3.59	0.10	0.30	17	>1
Recessive	1.74	0.25–12.11	0.58	0.04	69	1.62	0.85–3.11	0.14	0.35	6	>1
Dominant	0.90	0.42–1.94	0.79	0.009	79	1.43	0.96–2.11	0.08	0.23	33	>1
Codominant	0.99	0.46–2.14	0.98	0.0007	86	**1.36**	**1.01–1.83**	**0.04**	0.11	54	>1

OR: odds ratio; CI: confidence interval; p^A and p^B: p values for association and heterogeneity with significance set at < 0.05 and < 0.10, respectively; p_i: p values for tests of interaction after Bonferroni correction; Values in **bold** are significant in the tests of association.

Table 5. Subgroup OR associations of the M4 *CYP1A1* polymorphisms with breast cancer among Indian women.

		Premenopausal				Postmenopausal					
		n = 2				n = 2					
	OR	95% CI	p^A	p^B	I^2	OR	95% CI	p^A	p^B	I^2	p_i
Homozygous	3.70	0.73–18.63	0.11	0.67	0	4.77	0.93–24.41	0.06	0.96	0	>1
Recessive	3.63	0.72–18.30	0.12	0.74	0	4.59	0.90–23.44	0.07	0.99	0	>1
Dominant	1.16	0.70–1.90	0.56	0.13	56	1.61	0.84–3.11	0.15	0.30	6	>1
Codominant	1.26	0.81–1.95	0.30	0.23	31	**1.83**	**1.04–3.24**	**0.04**	0.23	30	>1

OR: odds ratio; CI: confidence interval; p^A and p^B: p values for association and heterogeneity with significance set at < 0.05 and < 0.10, respectively; p_i: p values for tests of interaction after Bonferroni correction; Values in **bold** are significant in the tests of association.

3.4. Sensitivity analysis

Direction of effects of the pooled ORs in M1 and M2 polymorphisms remained unchanged at increased risk with sensitivity treatment indicating that they were not materially altered suggesting robustness of our findings.

4. Discussion

With a combined sample size of 5981 (2821 cases and 3160 controls) in three *CYP1A1* polymorphisms, this meta-analysis points to evidence of overall associations between the M1, M2 and M4 polymorphisms and breast cancer among Indian women. However, this association was limited by between study heterogeneity. Its sources were examined with subgroup analysis. Stratifying the studies according to geography revealed the North India subgroup to be more heterogeneous than their Southern counterparts.

Three meta-analyses have addressed associations of the *CYP1A1* polymorphisms in breast cancer with mixed populations [4-6]. The following polymorphisms were investigated by Chen et al. [4] (M1 and M2), Yao et al. [6] (M1) and Sergentanis et al. [5] (M1, M2, M3 and M4).

Our meta-analysis differs from these three in that we examined the M1, M2 and M4 polymorphisms in the Indian population only enabling discernment of differences in effects between North and South Indians. The Indian population is the second largest in the world with diverse social, cultural, linguistic and biological features spread across a wide topography [32].

A fourth meta-analysis that focused on the M1 polymorphism addressed its effects in breast cancer among South Indians as a subgroup of four comparisons [33]. These effects indicated significant increased risk for up to 4-fold in all the genetic models they used, which was similar to our findings from five studies. The difference between that meta-analysis and ours was that our statistical comparison between the North and South Indian populations resulted in significant differential effects, protecting the former and placing the latter at risk.

The combination of population stratification leading to multiple comparisons and borderline significance of some associations open the possibility of false-positive findings [34]. Avoiding this problem warrants that the subpopulation be defined in terms of marker-allele frequencies and factors that influence disease such as geography. In this meta-analysis, we addressed population stratification in terms of differential allele frequencies between two distinct regions of India, which intensified significance.

Still, our study has been limited by the following: (i) given the multiplicity of comparisons for different genetic models, geography and menopausal status subgroups, and the unavoidable flexibility of choosing and defining the correlates, associations may have been detected by chance alone; (ii) low sample sizes of the component studies which translate to weak statistical power. But then, the point of meta-analysis is to combine studies resulting in increase of statistical power; (iii) that most of the studies were hospital-based may preclude extrapolation of our findings to the general population; (iv) heterogeneity of most of our findings, (v) deviation of some studies from the HWE which may have biased summary outputs and point to methodological weaknesses, such as biased selection of subjects, genotyping errors population stratification [35]. However, this was addressed with sensitivity analysis. (vi) Our study was based on unadjusted data, as the genotype information stratified for the main confounding variables was unavailable in the original papers. In addition, addressing of the confounding factors varied across the studies.

Yet, despite these weaknesses, the strengths of our meta-analysis include: (i) statistical homogeneity of the M4 homozygous and recessive effects imply combinability of the component studies; (ii) consistency of overall findings across the genetic models; (iii) because we confined our meta-analysis to a single country, we were able to delineate differential summary effects between populations of North and South India; (iv) controls were uniformly defined (cancer-free, healthy), minimizing non-differential misclassification bias.

The findings we report here highlight two points. The first is that individual epidemiological studies may lack statistical power or may have other interfering factors which prevent the unmasking of overall associations. Likewise, geographically local associations with specific alleles may exist which are due to linkage disequilibrium with other disease modifying alleles and are not reproduced in other populations. The second point is a caution with regard to drawing conclusions from individual studies. We report results that were not apparent from an examination of individual studies. We find that meta-analysis is a useful tool to examine broad trends in *CYP1A1* associations with breast cancer in Indian populations, and may avoid possible misleading conclusions based on only single-population studies.

The pathways of carcinogen metabolism are complex, mediated by the activities of multiple genes in concert with *CYP1A1* such as *GSTM1* [12]. It is conceivable that breast cancer risk related to any one locus will be small because gene-gene as well as gene-environment interactions are likely to operate. Individual studies in our meta-analysis have addressed gene-gene [7,12] and gene-environment [8,10,13] interaction and provided data which we excluded for concern with multiple testing issues.

5. Conclusion

To our knowledge, this is the first meta-analysis that details the association of *CYP1A1* polymorphisms with breast cancer among Indian women. This focus on one country allowed us to examine differences with use of geography and menopausal subgroups. Because our meta-analysis summary effects are relevant only to this demography, we provide an epidemiological profile of Indian

women's susceptibility to breast cancer on account of the *CYP1A1* polymorphisms. Additional well-designed studies based on sample sizes commensurate with detection of small genotypic risks should allow more definitive conclusions about the association of *CYP1A1* polymorphisms and breast cancer among Indian women.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary

Table S1. Genotype frequencies of the included studies that examine associations of the *CYP1A1* polymorphisms with breast cancer among Indian women.

	First author	Year	Indian Region	Case	Control	Case	Control	Case	Control	maf	HWE
	M1 (1151/1527)*			**TT**		**TC**		**CC**			
1	Singh N	2007	North	94	94	35	53	17	15	0.26	0.07
2	Singh V	2007	North	70	93	60	80	12	43	0.38	0.001
3	Chacko	2005	South	62	90	39	18	11	4	0.12	0.02
4	Syamala s	2010	South	93	243	87	106	39	18	0.19	0.22
5	Syamala f	2010	South	55	243	56	106	29	18	0.19	0.22
6	Naushad	2011	South	168	140	125	98	49	15	0.25	0.69
7	Kiruthiga	2011	South	30	36	17	12	3	2	0.16	0.45
	M2 (1039/1022)*			**AA**		**AG**		**GG**			
1	Singh N	2007	North	98	119	36	41	11	2	0.14	0.46
2	Singh V	2007	North	104	119	38	68	0	9	0.22	0.86
3	Surekha	2009	South	78	122	169	127	1	0	0.26	<0.001
4	Chacko	2005	South	67	90	34	19	11	3	0.11	0.13
5	Naushad	2011	South	221	144	108	99	13	10	0.24	0.16
6	Kiruthiga	2011	South	34	48	4	2	12	0	0.02	0.89
	M4 (631/611)*			**CC**		**CA**		**AA**			
1	Singh N	2007	North	129	145	12	15	6	2	0.06	0.04
2	Singh V	2007	North	93	43	43	52	6	2	0.14	0.24
3	Naushad	2011	South	274	240	68	13	0	0	0.03	0.03

* *CYP1A1* polymorphism (cases / controls); s: sporadic; f: familial; maf: minor allele frequency; HWE: Hardy-Weinberg Equilibrium *p* values.

Table S2. Genotype frequencies of the included studies that examine associations of the *CYP1A1* polymorphisms with breast cancer among Indian women stratified by menopausal status.

			Premenopausal								Postmenopausal							
First author	Year	Indian Region	Case	Control	Case	Control	Case	Control	maf	HWE	Case	Control	Case	Control	Case	Control	maf	HWE
M1			**TT**		**TC**		**CC**				**TT**		**TC**		**CC**			
N (cases/controls)			(279/309)								(230/251)							
Singh N	2007	North	40	57	17	21	5	3	0.17	0.55	50	30	18	21	13	8	0.31	0.18
Singh V	2007	North	53	58	43	35	9	13	0.31	0.35	17	35	17	35	3	10	0.34	0.79
Chacko	2005	South	29	44	58	58	25	0	0.35	0.14	33	46	54	54	25	12	0.35	0.51
M2			**AA**		**AG**		**GG**				**AA**		**AG**		**GG**			
N (cases/controls)			(277/309)								(232/251)							
Singh N	2007	North	39	51	16	29	5	1	0.19	0.16	56	49	23	9	4	1	0.09	0.45
Singh V	2007	North	80	70	25	41	0	5	0.22	0.74	24	49	13	27	0	4	0.22	0.91
Chacko	2005	South	31	45	57	58	23	9	0.34	0.10	36	45	57	58	23	9	0.34	0.10
M4			**CC**		**CA**		**AA**				**CC**		**CA**		**AA**			
N (cases/controls)			(168/197)								(118/139)							
Singh N	2007	North	57	70	3	10	2	1	0.07	0.37	66	54	9	4	6	1	0.05	0.02
Singh V	2007	North	67	83	34	32	4	1	0.15	0.27	36	59	9	20	2	1	0.14	0.63

maf: minor allele frequency; HWE: Hardy-Weinberg Equilibrium *p* values.

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