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EPIDEMIOLOGY

The association of SULT1A1 codon 213 polymorphism and breast cancer susceptibility: meta-analysis from 16 studies involving 23,445 subjects

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Abstract Epidemiological studies on the association between SULT1A1 codon 213 polymorphism and breast cancer risk are inconclusive. In order to derive a more precise estimation of the association, a meta-analysis was conducted in this article. Sixteen studies including 9,881 cases and 13,564 controls were collected for SULT1A1 codon 213 polymorphism by searching the databases of Medline, PubMed, Embase, and ISI Web of Knowledge. The strength of association between SULT1A1 codon 213 polymorphism and breast cancer susceptibility was assessed by calculating crude ORs with 95% CIs. When all the 21 studies were pooled into the meta-analysis, there was no evidence for significant association between SULT1A1 codon 213 polymorphism and breast cancer susceptibility (for Arg/Arg versus Arg/His: OR = 0.999, 95% CI = 0.941–1.061; for Arg/Arg versus His/His: OR = 1.121, 95% CI = 1.013–1.242; for dominant model: OR = 1.128, 95% CI = 1.01–1.26; for recessive model: OR = 1.151, 95% CI = 0.950–1.394). In the subgroup analysis by the source of controls, significant increased risk was found for hospital-based studies (for Arg/Arg versus Arg/His: OR = 1.173, 95% CI = 1.000–1.376; for Arg/Arg versus His/His: OR = 1.600, 95% CI = 1.134–2.256; for dominant model: OR = 1.269, 95% CI = 1.134–2.256; for recessive model: OR = 1.664, 95% CI = 1.070–2.588). In summary, the meta-analysis suggests that SULT1A1 codon 213 polymorphism may be associated with the hospital-based studies. However, large number of samples and representative hospital-based studies with homogeneous breast cancer patients and well-matched controls are warranted to confirm this finding.

Keywords SULT1A1 codon 213 · Polymorphism · Breast cancer · Meta-analysis

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Introduction

Breast cancer is the most common cancer in women: about 1.15 million new cases with 41,000 deaths were reported in 2002 [1]. In the United States, an estimated 203,500 new cases will be diagnosed and approximately 39,600 women will die from breast cancer [2]. The SULT1A1 gene that encodes the SULT1A1 enzyme has been located on chromosome 16p12.1–p11.2 [3], which has a common functional polymorphism, located in the coding region (638 G to A), resulting in a substitution of histidine for arginine ($Arg^{213}His$) [4–6]. SULT1A1 has also been shown to be highly expressed in breast cancer cell lines [7], which was associated with a decreased risk of recurrence or improved prognosis of breast cancer [8]. The sulfonation of estrogens was catalyzed by SULT1A1 to form water-soluble and biologically inactive estrogen sulfates, which reducing the level of estrogen exposure in their target tissues [9, 10]. Previous functional studies have demonstrated that the variant A allele is associated with significantly reduced sulfotransferase activity in platelets compared with the wild-type G allele [5, 6] The relevant SULT1A1 $Arg^{213}His$ single-nucleotide polymorphism studies have shown that ^{213}His allele is linked to cancer susceptibility in several cancers [11–15]. The specific role of SULT1A1 codon 213

polymorphism in breast cancer susceptibility has been the research focus of numerous researches [11, 16–30]. However, the results of these studies have also been inconclusive, partially maybe the possible small effect of the polymorphism on breast cancer risk and the relatively small sample size in each of the published studies. Therefore, we performed this meta-analysis to derive a more precise estimation of the association between the SULT1A1 codon 213 polymorphism and the susceptibility for developing breast cancer.

Methods

Publication search

Medline, PubMed, Embase, and Web of Science (updated to April 20, 2010) were searched using the following search terms: "SULT1A1," "Codon 213," "polymorphism," or "genotype" and "breast." To search as many articles as possible, the relevant publications' references were carefully evaluated. Only those published studies with full-text articles in English and Chinese were included in this meta-analysis. For overlapping and republished studies, only the first published or the study with the largest samples was included.

Selection criteria

The selection criteria were (1) evaluation the polymorphism of SULT1A1 Codon 213 and breast cancer risk, (2) case–control studies, (3) with sufficient published data to estimate an odds ratio (OR) with 95% confidence interval (CI), (4) written in English and Chinese language, (5) executing Hardy–Weinberg equilibrium in the control group ($P < 0.01$). The selected articles should meet all of the above criteria.

Data extraction

The relevant information was extracted from all selected articles independently by two of the authors (Yanlei Ma and Jianjun Yang) according to the above-mentioned inclusion criteria. The following data were extracted from each study: first author's name, year of publication, countries which human samples came from, ethnicity, source of controls, total number of cases and controls, and numbers of cases and controls with the SULT1A1 Codon 213 polymorphism, respectively. Different ethnicities were categorized as Caucasian, Asian, and mixed. Study design was stratified to population-based studies, hospital-based studies. Any minimum number of patients to include was not defined in the current meta-analysis.

Statistical methods

Crude ORs with 95% CIs were used to assess the strength of association between the polymorphism of SULT1A1 Codon 213 and breast cancer risk. The pooled ORs were performed for co-dominant model (Arg/Arg versus Arg/His, Arg/Arg versus His/His), dominant model (His/Arg + His/His versus Arg/Arg), and recessive model (His/His versus His/Arg + Arg/Arg), respectively. Heterogeneity assumption was checked by the chi-square-based Q-test [31]. A P-value greater than 0.10 for the Q-test demonstrates a lack of heterogeneity among studies, so the pooled OR estimate of each study was calculated through the fixed-effects model (the Mantel–Haenszel method) [32]. Otherwise, the random-effects model (the DerSimonian and Laird method) was used [33]. Sensitivity analysis was performed to assess the stability of the results. Subgroup analysis was performed by ethnicity and study design. Each study involved in the meta-analysis was deleted each time to reflect the influence of the individual dataset to the pooled ORs [34]. An estimate of potential publication bias was executed by the funnel plot, where the standard error of log (OR) of each study was plotted against its log (OR). The significance of the intercept was determined by the t-test suggested by Egger ($P < 0.05$ was considered the representative of statistically significant publication bias) [35]. All the statistical tests were performed with STATA version 10.0 (Stata Corporation, College Station, TX, USA).

Results

Study characteristics

Our database search generated a total of 16 publications that met the inclusion criteria. In one of these publications, ORs were presented separately for each subgroup, so for all publications we considered each group separately for subgroup analysis. Hence, a total of 16 studies including 9,881 cases and 13,564 controls were involved in this meta-analysis. Table 1 lists the characteristics of each study. There were seven studies of Caucasians, seven of Asians, one study of mixed populations, and one study of not reported populations. Almost all cases were pathologically confirmed. Controls were primarily healthy individuals that were matched for age. Among these 16 studies, 8 were population-based, 7 were hospital-based, and 1 was mixed population.

Main results

When all the studies were pooled, no significant associations were found between the $Arg^{213}His$ polymorphism and

Table 1 Main characteristics of studies included in the meta-analysis

First author	Year	Country	Ethnicity	Source of controls	Total cases/controls	Genotypes distribution (case/control)			HWE
						Arg/Arg	Arg/His	His/His	
Syamala	2010	India	Asian	HB	359/367	254/271	87/90	18/6	Y
Chang	2010	Germany	Caucasian	PB	3139/5426	1381/2338	1332/2430	426/658	Y
Gulyaeva	2008	Russia	Caucasian	PB	82/180	23/63	40/61	19/56	Y
Hu	2006	China	Asian	HB	209/426	160/355	41/61	8/10	Y
Cheng	2005	Taiwan	Asian	HB	468/740	439/693	27/47	2/0	Y
Choi	2005	Korea	Asian	Mixed	986/1045	796/830	190/215	0/0	Y
Jerevall	2005	Sweden	Caucasian	PB	229/228	80/84	121/106	28/38	Y
Le Marchand	2005	USA	Mixed	PB	1339/1370	801/782	424/484	114/104	Y
Lilla	2005	Germany	Caucasian	PB	419/884	198/374	169/403	52/107	Y
Yang	2005	China	Asian	PB	1102/1147	921/977	181/170	0/0	Y
Chacko	2004	India	Asian	HB	140/140	76/95	56/41	8/4	Y
Han	2004	China	Asian	HB	209/426	160/355	41/61	8/10	Y
Langsenlehner	2004	Austria	Caucasian	PB	498/499	201/224	250/212	47/63	Y
Tang	2003	USA	NS	HB	103/133	50/79	42/47	11/7	Y
Zheng	2001	USA	Caucasian	PB	155/326	55/147	71/135	29/44	Y
Seth	2000	USA	Caucasian	HB	444/227	229/110	176/94	39/23	Y

PB population-based study, *HB* hospital-based study, *HWE* Hardy–Weinberg equilibrium, *Y* yes

breast cancer risk (His/Arg versus Arg/Arg: OR = 0.999, 95% CI = 0.941–1.061, $P = 0.001$ for heterogeneity; His/His versus Arg/Arg: OR = 1.121, 95% CI = 1.013–1.242, $P = 0.012$ for heterogeneity; His/Arg + His/His versus Arg/Arg: OR = 1.128, 95% CI = 1.01–1.26, $P = 0.001$ for heterogeneity; His/His versus His/Arg + Arg/Arg: OR = 1.151, 95% CI = 0.950–1.394, $P = 0.012$ for heterogeneity). However, in the stratified analysis by control sources, significant associations were observed in HB (His/Arg versus Arg/Arg: OR = 1.173, 95% CI = 1.000–1.376, $P = 0.181$ for heterogeneity; His/His versus Arg/Arg: OR = 1.600, 95% CI = 1.134–2.256, $P = 0.125$ for heterogeneity; His/Arg + His/His versus Arg/Arg: OR = 1.269, 95% CI = 1.036–1.555, $P = 0.112$ for heterogeneity; His/His versus His/Arg + Arg/Arg: OR = 1.664, 95% CI = 1.070–2.588, $P = 0.194$ for heterogeneity). To the contrary, no significant associations were detected in PB. Otherwise, in the stratified analysis by ethnicity, no significant associations were observed for all comparison models (Table 2).

Sensitivity analysis and publication bias

In overall studies, the results suggested that no significant influence of any of the individual dataset to the pooled OR values was observed. Begg's funnel plot and Egger's test similarly failed to reveal evidence of publication bias (data not shown).

Discussion

Although a number of recent studies [11, 16–31] have reported a significant association between the $Arg^{213}His$ polymorphism and breast cancer risk, others have found no such association. In order to resolve this conflict, we initiated this meta-analysis of 16 studies, involving 9,881 cases and 13,564 controls, so as to derive a more precise estimation of the exist or absence of this association.

We found that polymorphism in $Arg^{213}His$ of the SULT1A1 gene displayed no significant association with breast cancer risk, either when the included study populations were pooled or when they were subjected to a stratified analysis according to ethnicity. The latter result suggests that differences in genetic background and living environment do not influence any potential association between the $Arg^{213}His$ polymorphism and breast cancer risk. However, the current results indicated that significantly increased breast cancer risk in $Arg^{213}His$ of the SULT1A1 were found for the hospital-based studies but not in population-based studies. Therefore, using a proper and representative hospital-based control subjects is very important to reduce biases in such genetic association studies.

Two advantages of our study were the large number of samples included and our failure to find a significant association in any of the genetic models tested. However, some limitations were acknowledged. First of all, the

Table 2 Meta-analysis of SULT1A1 Arg213His polymorphism and breast cancer risk

Study groups	His/Arg versus Arg/Arg		His/His versus Arg/Arg		Dominant model		Recessive model	
	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
Total	0.999 (0.941–1.061)	0.001	1.121 (1.013–1.242)	0.012	1.128 (1.01–1.26)	0.001	1.151 (0.950–1.394)	0.012
Ethnicity								
Caucasia	0.987 (0.914–1.065)	0.003	1.072 (0.957–1.201)	0.028	1.109 (0.935–1.316)	0.004	1.005 (0.797–1.268)	0.014
Asian	1.104 (0.977–1.246)	0.126	2.372 (1.463–3.845)	0.788	1.200 (1.007–1.430)	0.079	2.136 (1.308–3.488)	0.738
Source								
HB	1.173 (1.000–1.376)	0.181	1.600 (1.134–2.256)	0.125	1.269 (1.036–1.555)	0.112	1.664 (1.070–2.588)	0.194
PB	0.978 (0.914–1.047)	0.001	1.082 (0.973–1.205)	0.039	1.087 (0.948–1.247)	0.003	1.042 (0.848–1.280)	0.017

P_h *P*-value of *Q*-test for heterogeneity test, *PB* population-based study, *HB* hospital-based study

controls in the included studies were not uniformly determinated, such that the control subjects in different studies might have had varying risks of developing breast cancer. Secondly, the results presented here are based on unadjusted estimates. A more precise analysis could be guided if more detailed individual data were available which allowed it to be adjusted according other covariates such as age, smoking and drinking status, menopausal status, lifestyle, basal metabolic index, obesity, and environmental factors.

In conclusion, this meta-analysis suggests that SULT1A1 Codon 213 polymorphism may be associated with the hospital-based studies. However, large number of samples and representative hospital-based studies with homogeneous breast cancer patients and well-matched controls are warranted to confirm this finding. Future studies should extend this investigation by incorporating other potential risk factors for breast cancer.

Conflict of interest statement None of the authors of this study has any applicable conflict of interest.

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