

LSP1 Gene rs3817198 Polymorphism and Breast Cancer Risk: A Systematic Review and Meta-analysis Study

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Abstract

In this meta-analysis, we tried to clear the relationship between breast cancer risk and LSP1 gene rs3817198T>C polymorphism. This meta-analysis was conducted according to PRISMA protocol. We searched PubMed/Medline, Web of sciences and EMBASE. All literature investigating the association of LSP1 gene rs3817198T>C and breast cancer risk were considered to include in the meta-analysis. We pooled ORs using both fixed and random-effect models. Egger's test and funnel plot were used to evaluate Publication bias and small study effect. After evaluation and screening of citations, 14 publications were eligible for final analysis after applying of inclusion and exclusion criteria. Overall, 30,204 cases and 35,282 controls included in this meta-analysis. There was the significant association between LSP1 gene rs3817198T>C polymorphism and breast cancer only in homozygote genetic model (OR=1.14 [1.05-1.24]) and no association was found in heterozygotes (OR=1.03 [0.98-1.07]). The association was significant for population-based studies and European & American & African population in both homozygote and heterozygote genetic model. There was no evidence of bias of literature and no small study effect. In conclusion, it seems that LSP1 gene rs3817198 polymorphism play its role in breast cancer incidence and other SNPs and environment are such triggers. Nevertheless, we recommend genome-wide association studies to evaluate the effect of SNPs in combination, not as single SNPs.

Keywords: rs3817198- breast cancer risk- meta-analysis study

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Introduction

Breast cancer accounts as the most frequent type of cancer among women and the incidence of breast cancer are rapidly increasing, particularly in developing countries. Breast cancer arises from the effect of both genetic and environmental factors [1]. Although, the role of single nucleotide polymorphisms (SNPs) in the incidence of breast cancer has been shown in many studies [2-5], 30-40% of the familial and only 3-4% of the total number of breast cancer cases attributed to genetic component [6].

Leukocyte-specific protein 1 (LSP1) gene encoding an F-actin binding protein is located on 11p15.5. Studies investigating association LSP1 gene rs3817198T>C and

breast cancer risk showed different results. However, there most of the studies showed no association between rs3817198 SNP and breast cancer [7-9], but there is evidence of increased [10-11] or may be decreased risk of breast cancer [12]. In this meta-analysis, we tried to clear the relationship between breast cancer risk and LSP1 gene rs3817198T>C polymorphism.

Materials Methods

Literature identification

This meta-analysis was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol. In order to retrieve all studies related to LSP1 gene and breast

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cancer, a complete search of databases was performed. We searched PubMed/Medline, Web of sciences and EMBASE using phrases “LSP”, “LSP1”, “lymphocyte-specific protein”, “WP34” and “breast cancer”, “breast tumor”, and “breast neoplasm”. Detailed search strategy of databases is provided in supplementary Table 1. The additional search of the Reference list of final retrieved studies and related meta-analyses was carried out to include missed citations.

Study selection

All literature investigating the association of LSP1 gene rs3817198T>C and breast cancer risk were considered to include in the meta-analysis. We excluded studies if they had the following criteria: (1) studies evaluating different polymorphisms of LSP1 gene; (2) studies had no control group; (3) studies providing no measure of association or information for calculation odds ratio (OR); (4) studies presenting only per-allele OR, not for four genetic models; (5) studies with breast cancer mortality and benign breast disease as main outcome; (6) case report and animal studies.

Data extraction

Screening of citations and extraction of the required information was carried out independently by two authors (ASM, MR). The following information was collected from included studies: name of first author, publication date, study design, source of controls (population-based or hospital-based), considered confounders in each models, genotyping methods, population ethnicity, total number of cases and controls, minor allele frequency and OR and their reported 95% confidence interval (CI) for homozygote and heterozygote inheritance models.

Study qualification

Four items, which might interfere with the results of the meta-analysis, including 1) source of a control group, 2) ethnicity, 3) menopausal status, and 4) sample size was considered to assess the quality of included studies. Quality of studies based on mentioned four items is presented in Supplementary Table 2.

Statistics

Allelic frequency of controls calculated for studies separately. Calculated frequencies of the LSP1 gene rs3817198T>C genotype was evaluated for Hardy–Weinberg equilibrium using the X² statistic. We pooled ORs using both fixed and the DerSimonian and Laird random-effects models. Heterogeneity across studies was assessed using Q and I² statistics [13-14]. An I² value above 75% at a significance level of < 0.1 was considered as presence of statistically significant heterogeneity [15]. Egger’s test and contour-enhanced funnel plot were used to evaluate Publication bias and small study effect [16]. The measure of association of all genetic inheritance models including TT versus CC (homozygote) and TC vs. CC (heterozygote) was assessed. Additional subgroup analysis was performed for ethnicity, and study setting. The ethnicity subgroup was defined based on the continent

as Asians and Europeans & North Americans & Africans. Subgrouping included population-based (those reported a population-based case-control or nested case-control) and hospital-based (those reported a hospital-based case-control). All analyses were performed using Stata version 13 (Stata Corp LP, College Station, TX, USA).

Results

Selected literature

Through the primary search of the literature, 287 citations were identified. After evaluation and screening of citations, 29 publications considered for complete assessment of full-text. fourteen publications were eligible for final analysis after applying of inclusion and exclusion criteria [7-12, 17-24]. Figure one display the screening process. Studies conducted by Barnholtz-Sloan (African-American & white) and Garcia-Closas (ER-positive & ER-negative) [12, 20] were considered as two separate studies each because provided ORs for two different populations. Table 1 shows adjusted and unadjusted OR for every single study. From fourteen, eleven had a population-based source of control. Five literatures were conducted in Europe, one in North America, six in Asia and one in Africa. Overall, 30,204 cases and 35,282 controls included in this meta-analysis. Detailed characteristic of included studies and reason of exclusion of others are provided in supplementary Table 3 and 4.

Analysis

In the overall analysis, there was a significant association between LSP1 gene rs3817198T>C polymorphism and breast cancer only in homozygote genetic model (OR=1.14 [1.05-1.24], Figure 2) and no association was found in heterozygotes (OR=1.03 [0.98-1.07], Figure 3). In the subgroup analysis by the source of controls and ethnicity,

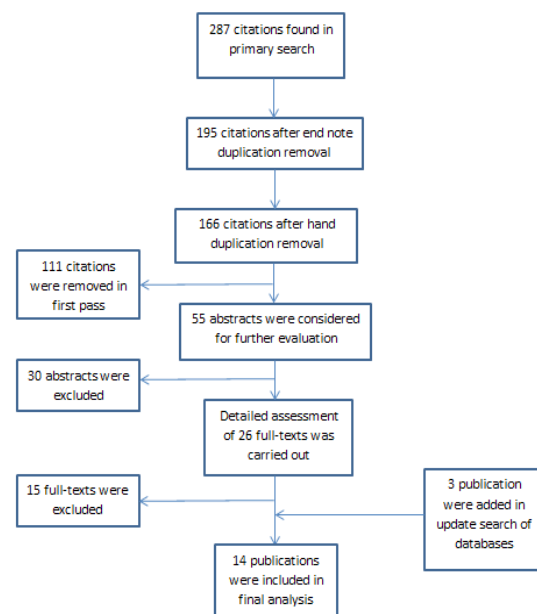


Figure 1. Flowchart Diagram of Selection Process

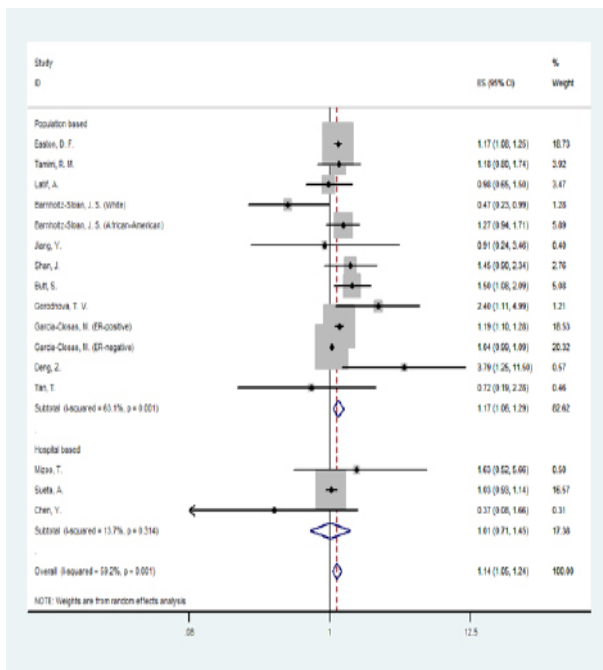


Figure 2. Random Effect Model Meta-Analysis of LSP1 Gene Rs3817198 Polymorphism for Homozygote Genetic Models and Risk of Breast Cancer. the Effect Size is Odds Ratio

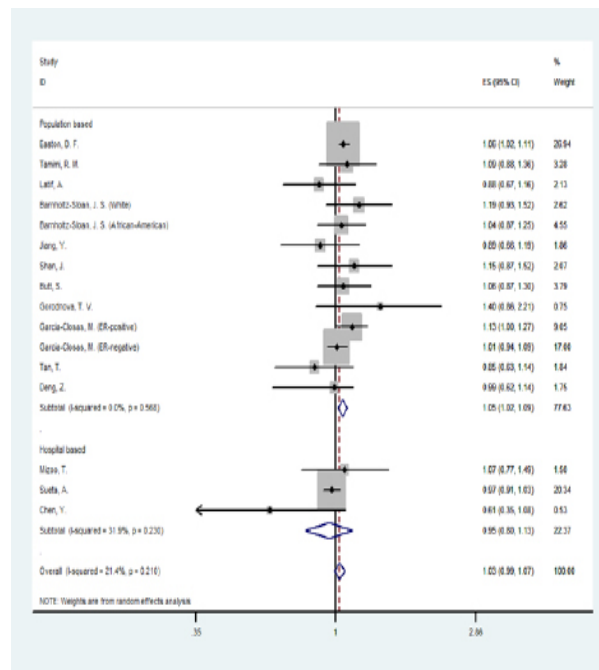


Figure 3. Random Effect Model Meta-Analysis of LSP1 Gene Rs3817198 Polymorphism for Heterozygote Genetic Models and Risk of Breast Cancer. the Effect Size is Odds Ratio

Table 1. Adjusted and Unadjusted Odds Ratio of Studies Assessing the Association Between LSP1 (Rs 3817198) Polymorphism and Breast Cancer

First author	Year	Menopausal status	Heterozygote		Homozygote	
			Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)
Easton, D. F.	2007	Mix	1.06 (1.02-1.11)	-	1.17 (1.08-1.25)	-
Garcia-Closas, M. (ER-positive)	2008	Mix	1.13 (1.00-1.27)	-	1.19 (1.10-1.28)	-
Garcia-Closas, M. (ER-negative)	2008	Mix	1.01 (0.94-1.09)	-	1.04 (0.99-1.09)	-
Barnholtz-Sloan, J. S. (African-American)	2010	Mix	1.19 (0.93-1.52)	-	0.47 (0.23-0.99)	-
Barnholtz-Sloan, J. S. (White)	2010	Mix	1.04 (0.87-1.25)	-	1.27 (0.94-1.71)	-
Gorodnova, T. V.	2010	Mix	-	1.40 (0.86-2.21)	-	2.40 (1.11-4.99)
Latif, A.	2010	Mix	0.88 (0.67-1.16)	-	0.98 (0.65-1.50)	-
Tamimi, R. M.	2010	Mix	1.09 (0.88-1.36)	-	1.18 (0.80-1.74)	-
Jiang, Y.	2011	Mix	0.89 (0.66-1.19)	-	0.91 (0.24-3.46)	-
Sueta, A.	2011	Mix	0.97 (0.91- 1.03)	-	1.03 (0.93-1.14)	-
Butt, S.	2012	Mix	1.06 (0.87-1.30)	1.09 (0.90-1.33)	1.50 (1.08-2.09)	1.53 (1.10-2.11)
Shan, J.	2012	Mix	1.15 (0.87-1.52)	-	1.45 (0.90-2.34)	-
Mizoo, T.	2013	Mix	1.07 (0.77-1.49)	1.14 (0.85-1.55)	1.63 (0.52-5.66)	2.04 (0.72-6.60)
		Pre	1.00 (0.60-1.68)	0.92 (0.58-1.48)	3.29 (0.42-68.89)	3.98 (0.58-78.39)
		Post	1.18 (0.75-1.86)	1.30 (0.87-1.94)	1.39 (0.32-6.31)	1.65 (0.46-6.55)
Chen, Y.	2016	Mix	0.61 (0.35-1.08)	-	0.37 (0.08-1.66)	-
Deng, Z.	2016	Mix	0.99 (0.62-1.58)	-	3.79 (1.25-11.50)	-
Tan, T.	2016	Mix	-	0.85 (0.63-1.14)*	-	0.72 (0.19-2.28)*

Year, year of publication; OR, odds ratio; CI, confidence interval; *ORs calculated by authors via STATA software

Table 2. Subgroup Meta-Analysis of LSP1 R3817198 Polymorphism and Breast Cancer Risk

Subgroup	Studies No.	Homozygote				Heterozygote							
		Fixed model OR (95% CI)	Random model OR (95% CI)	P _h	I ₂	T ₂	Fixed model OR (95% CI)	Random model OR (95% CI)	P _h	I ₂	T ₂		
Overall	16	1.10 (1.07-1.14)	1.14 (1.05-1.24)	0	59.2	0.01	16	1.03 (1.00-1.06)	1.03 (0.98-1.07)	0.21	21.4	0	
Control source													
Hospital based	3	1.03 (0.93-1.14)	1.01 (0.71-1.46)	0.31	13.7	0.04	3	0.97 (0.91-1.03)	0.95 (0.80-1.13)	0.23	31.9	0.01	
Population based	13	1.11 (1.07-1.15)	1.17 (1.06-1.29)	0	63.1	0	13	1.05 (1.02-1.09)	1.05 (1.02-1.09)	0.57	0	0	
Continent													
Europe_america_africa	8	1.18 (1.11-1.27)	1.22 (1.03-1.44)	0.07	47.4	0.02	8	1.06 (1.02-1.10)	1.06 (1.02-1.10)	0.74	0	0	
Asia	6	1.04 (0.94-1.15)	1.13 (0.70-1.81)	0.16	37.1	0.12	6	0.96 (0.91-1.02)	0.96 (0.91-1.02)	0.56	0	0	

OR, odds ratio; CI, confidence intervals; P_h, P values of Q-test for heterogeneity test; I₂, I-square; T₂, Tau-square

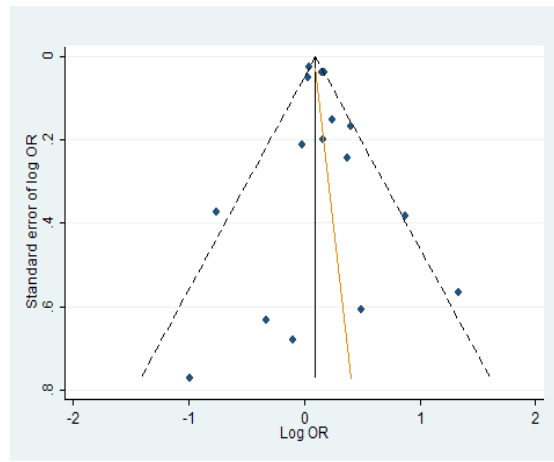


Figure 4. Funnel Plot for Homozygote Genetic Model with Regression Line Corresponding to the Egger's Regression Test for Funnel-Plot Asymmetry

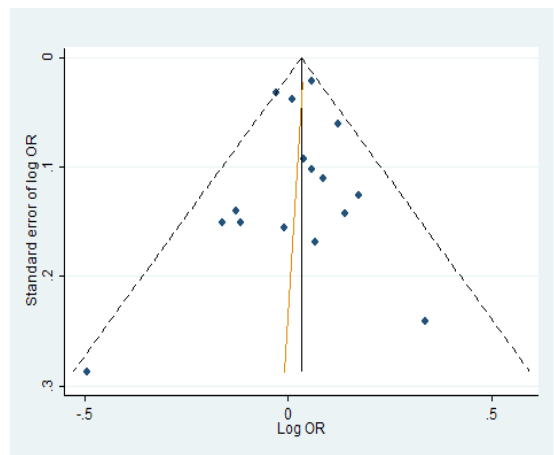


Figure 5. Funnel Plot for Heterozygote Genetic Model with Regression Line Corresponding to the Egger's Regression Test for Funnel-Plot Asymmetry

the significant association was found for population-based studies and European & American & African population in both homozygote and heterozygote genetic model. Nevertheless, results showed no relationship in Asians and hospital-based studies. The result of meta-analysis is presented in Table 2.

Publication bias

We evaluated publication bias by mean of Begg's funnel plot and Egger's test and there was no evidence of bias of literature and no small study effect (Figures 4 and 5).

Discussion

Genetic predisposition to breast cancer has been studied in many studies and some have proved the role of some SNPs in the incidence of breast cancer. LSP1 gene encodes an F-actin binding protein, which helps in neutrophil migration and chemotaxis [25]. The linkage between LSP1 gene rs3817198T>C mutation and breast

cancer has been evaluated in several literatures, but there is no unanimity in the results. Some showed no association between LSP1 gene rs3817198 polymorphism and breast cancer [8] and some revealed increased risk of breast cancer coming with the polymorphism [10]. To bring together all the information, we conducted this meta-analysis to evaluate the association between LSP1 gene rs3817198 polymorphism and breast cancer in different designs and ethnicities and update the previous meta-analysis. Overall, we found that LSP1 gene rs3817198 polymorphism is associated with breast cancer only in homozygote genetic model. In subgroup analysis, the association was significant in population-based studies and European & American & African population in both homozygote and heterozygote genetic model.

The association between breast cancer and LSP1 gene rs3817198 polymorphism was only significant in homozygote genetic model, which was consistent with results of two previous meta-analyses [26-27]. This result demonstrates that minor allele carries the risk of breast cancer. In subgroup analysis, we found the significant association for European & American & African population not Asian in both genetic models. The most recent meta-analysis [27] showed the same results but the earlier [26] documented the association only in homozygote genetic model. Although we categorized the population according to the continent and the two previous meta-analyses based on ethnicity, it makes sense that they considered European and Americans as Caucasian. Association between LSP1 gene rs3817198 polymorphism and breast cancer in European & American & African population, not Asian support the role of environment and also the possibility of the existence of concomitant SNPs. In addition, the association remained significant just in population-based studies. Nevertheless, this association was not seen in two mentioned studies. The diversity is probably because we included more studies and besides, we took nested case-control as population-based studies. As we know, the risk of bias is lower in population-based studies, so their results are more reliable. Significant association in population-based studies confirms the main results of this meta-analysis.

This paper faced some limitation. First, some studies did not provide adjusted ORs and we analyzed both adjusted and unadjusted ORs together. Second, due to lack of information, we were not able to perform subgroup analysis for menopausal status and other risk factors.

In conclusion, it seems that LSP1 gene rs3817198 polymorphism play its role in breast cancer incidence and other SNPs and environment are such triggers. Nevertheless, we recommend genome-wide association studies to evaluate the effect of SNPs in combination, not as single SNPs.

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