

Dominant and Recessive Genetic Models of LSP1 Gene rs3817198 Polymorphism and Breast Cancer Risk: A Systematic Review and Meta-analysis Study

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Abstract

Objective: The aim of this meta-analysis was to discover the effect of dominant and recessive genetic models of LSP1 gene rs3817198 polymorphism on breast cancer risk. **Material and Method:** We performed this meta-analysis according to PRISMA protocol. Three databases, including PubMed/Medline, Web of sciences, and EMBASE were searched. In this meta-analysis, we included all studies that evaluated the association between LSP1 gene rs3817198 and breast cancer risk. ORs and their reported 95% confidence interval (CI) for dominant and recessive inheritance models were extracted from final retrieved studies. ORs were pooled using both fixed and the random-effect models. Egger's test and contour-enhanced funnel plot were used to evaluate publication bias and small study effect. Twelve publications were eligible for final analysis after observing our defined inclusion and exclusion criteria. **Results:** Totally, this meta-analysis composed of 15,530 cases and 20,258 controls. This study revealed a significant association between LSP1 gene rs3817198 polymorphism and breast cancer in the dominant genetic model (OR=1.07 [1.01-1.14]). Inversely, no association was found in the recessive genetic model (OR=1.10 [0.93-1.32]). Subgroup analysis displayed a significant association in population-based studies and European & American and African population only in the dominant genetic model. Begg's funnel plot and Egger's test revealed no publication bias. **Conclusion:** According to our findings, it seems that LSP1 gene rs3817198 polymorphism is associated with breast cancer risk and this risk is more prominent in Caucasians.

Keywords: LSP1 gene- polymorphism- breast cancer- meta-analysis

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Introduction

Breast cancer is the most common cancer among women and it is the second cause of cancer-related death. Environmental exposure along with genetic pre-disposition has been shown to have a cumulative effect on breast cancer risk [1]. Genetic component is responsible for 30-40% of familial and only 3-4% of the total number of breast cancer cases [2]. Recently, there has been a real effort to prove the role of single nucleotide polymorphisms (SNPs) in breast cancer risks [3-5].

Leukocyte-specific protein 1 (LSP1) gene is located on 11p15.5 and encodes an F-actin binding protein. LSP1

gene rs3817198T>C polymorphism has been studied in many kinds of literature. Several studies showed no association between rs3817198 SNP and breast cancer [6-8], but there are pieces of evidence on the relationship between rs3817198 SNP and increased [9-10] or maybe decreased risk of breast cancer [11]. The aim of this meta-analysis was to predict the effect of dominant and recessive genetic models of LSP1 gene rs3817198 polymorphism on breast cancer risk.

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Materials and Methods

Literature identification

We performed this meta-analysis according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol. Three databases, including PubMed/Medline, Web of sciences, and EMBASE were searched not to miss any study. We employed phrases “LSP”, “LSP1”, “lymphocyte-specific protein”, “WP34” and “breast cancer”, “breast tumor”, and “breast neoplasm” for our search. Process of databases search is provided in supplementary Table 1. Reference list of final included studies and related meta-analyses were additionally searched for any possible missed citations.

Study selection

We included all studies that evaluated the association between LSP1 gene rs3817198 and breast cancer risk in this meta-analysis. The exclusion criteria were: (1) evaluation of different polymorphisms of LSP1 gene; (2) no control group; (3) no measure of association or unavailable information for calculation odds ratio (OR); (4) breast cancer mortality and benign breast disease as main outcome; and (5) case report and animal studies.

Data extraction

Two authors (ASM, MR) independently screened citations and took all needed information. Name of first author, publication date, study design, source of controls (population-based or hospital-based), considered confounders in each model, genotyping methods, population ethnicity, total number of cases and controls, minor allele frequency and OR and their reported 95% confidence interval (CI) for dominant and recessive inheritance models were extracted from final retrieved studies.

Study qualification

In order to assess the quality of included studies, we considered four items including 1) source of the control group, 2) ethnicity, 3) menopausal status, and 4) sample size. Quality of studies based on mentioned four items is presented in supplementary Table 2.

Statistics

Minor Allele frequency for cases and controls were calculated for each study separately. The X² statistic was used for Hardy–Weinberg equilibrium based on calculated frequencies of the LSP1 gene rs3817198 genotype. ORs were pooled using both fixed and the random-effect models. Heterogeneity across studies was evaluated by mean of Q and I² statistics [12-13]. An I² value above 75% at a significance level of < 0.1 was considered as presence of statistically significant heterogeneity [14]. Egger’s test and contour-enhanced funnel plot were used to evaluate publication bias and small study effect [15]. The association of genetic inheritance models including dominant and recessive was assessed. Ethnicity and study setting were analyzed as subgroups. The ethnicity subgroup was defined based on the continent as Asians,

Europeans, North Americans, and Africans. Subgroups were population-based (those reported a population-based case control or nested case-control) and hospital-based (those reported a hospital-based case-control). We employed Stata version 13 (Stata Corp LP, College Station, TX, USA) for all analyses.

Results

Selected literature

Our primary search yielded 287 citations, full-text of 26 publications were precisely assessed after evaluation and screening of citations. Twelve publications were eligible for final analysis after observing inclusion and exclusion criteria [7, 8, 10, 11, 16-23]. Flowchart of the screening process is provided in Figure 1. Studies conducted by Barnholtz-Sloan (African-American and white) [11] was considered as two separate studies, because they provided ORs for two separate populations. Nine of studies had a population-based source of control. Four studies were conducted in Europe, one in North America, five in Asia, and one in Africa. Totally, this meta-analysis composed of 15,530 cases and 20,258 controls. Detailed characteristics of included and excluded studies are provided in supplementary Tables 3 and 4.

Analysis

The main analysis of this study revealed a significant association between LSP1 gene rs3817198 polymorphism and breast cancer in the dominant genetic model (OR=1.07 [1.01-1.14], Figure 2). Inversely, no

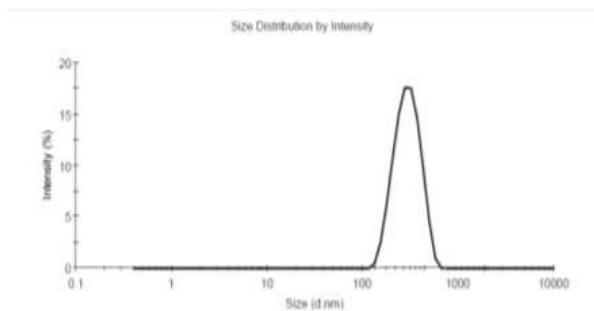


Figure 1. Flowchart Diagram of Selection Process

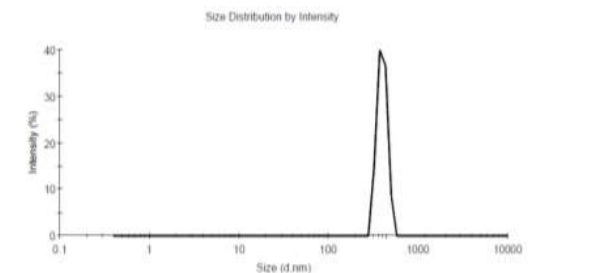


Figure 2. Random Effect Model Meta-Analysis of LSP1 Gene rs3817198 Polymorphism for Dominant Genetic Models and Risk of Breast Cancer. The Effect Size is Odds Ratio

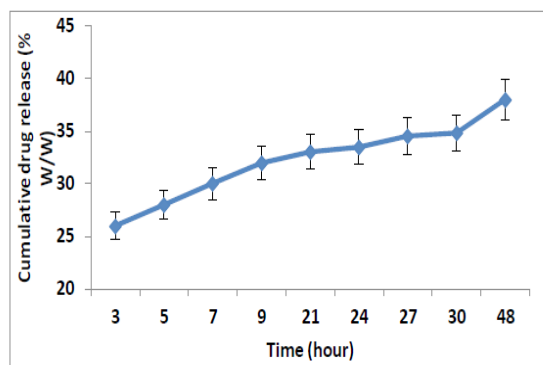


Figure 3. Random Effect Model Meta-Analysis of LSP1 Gene rs3817198 Polymorphism for Recessive Genetic Models and Risk of Breast Cancer. The Effect Size is Odds Ratio

association was found in the recessive genetic model (OR=1.10 [0.93-1.32], Figure 3). Additional subgroup analysis using the source of controls and ethnicity displayed a significant association in population-based studies and European and American and African population only in the dominant genetic model. However, the results on the recessive model indicated no relationship between breast cancer and LSP1 gene rs3817198 polymorphism. Table 2 presents complete outcome of this meta-analysis.

Publication bias

Begg's funnel plot and Egger's test were used for the assessment of publication bias, confirming no publication

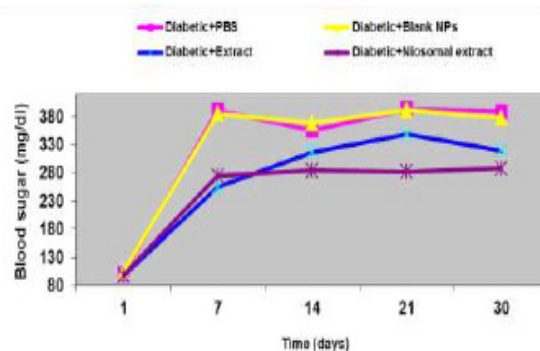


Figure 4. Funnel Plot for Dominant Genetic Model with Regression Line Corresponding to the Egger's Regression Test for Funnel-Plot Asymmetry

bias (Figure 4 and 5).

Discussion

Cancer is one of the leading causes of morbidity and mortality. During years, SNPs are always accused of synergic effects on cancer incidence. Many attempts have been made to clarify the role of SNPs in breast cancer risk [4-11, 24] and it is still a topic of debate. LSP1 gene is contributing in the production of an F-actin binding protein, which is expressed lymphocytes, neutrophils, and endothelial cells. LSP1 gene rs3817198 polymorphism is one of the SNPs that have been studied in many kinds of literature and different results have come out [11-16, 19]. This paper tried to integrate all available data and make

Table 1. Adjusted and Unadjusted Odds Ratio of Studies Assessing the Association between Dominant and Recessive Genetic Model of LSP1 (rs 3817198) Polymorphism and Breast Cancer

First author	Year	Menopausal status	Dominant		Recessive	
			Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)
Barnholtz-Sloan, J. S. (African-American)	2010	Mix	-	1.07 (0.85-1.35)*	-	0.43 (0.19-0.91)*
Barnholtz-Sloan, J. S. (White)	2010	Mix	-	1.07 (0.91-1.27)*	-	1.25 (0.95-1.66)*
Gorodnova, T. V.	2010	Mix	-	1.55 (0.97-2.49)*	-	2.02 (0.93-4.46)*
Latif, A.	2010	Mix	-	0.90 (0.69-1.17)*	-	1.04 (0.69-1.60)*
Tamimi, R. M.	2010	Mix	-	1.10 (0.89-1.36)*	-	1.13 (0.76-1.68)*
Campa, D.	2011	Mix	1.16 (0.94-1.43)	-	1.45 (0.81-2.57)	-
Sueta, A.	2011	Mix	-	1.01 (0.91-1.11)*	-	0.95 (0.89-1.00)*
Butt, S.	2012	Mix	-	1.16 (0.96-1.40)*	-	1.47 (1.06-2.03)*
Shan, J.	2012	Mix	-	1.20 (0.92-1.57)*	-	1.30 (0.82-2.10)*
Mizoo, T.	2013	Mix	-	1.18 (0.87-1.61)*	-	1.97 (0.60-7.43)*
		Pre	-	-	-	-
		Post	-	-	-	-
Chen, Y.	2016	Mix	-	0.41 (0.04-1.80)*	-	0.58 (0.32-1.01)*
Deng, Z.	2016	Mix	1.14 (0.73-1.77)	-	3.80 (1.26-11.49)	-
Tan, T.	2016	Mix	-	0.74 (0.20-2.35)*	-	0.84 (0.63-1.13)*

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

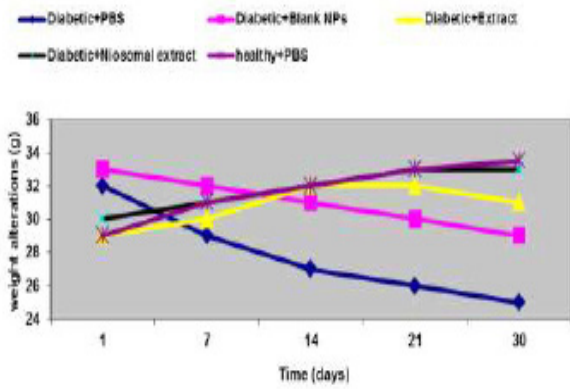


Figure 5. Funnel Plot for Recessive Genetic Model with Regression Line Corresponding to the Egger's Regression Test for Funnel-Plot Asymmetry

it clear to readers that whether there is an association between LSP1 gene rs3817198 polymorphism and breast cancer or not.

We found a significant association between LSP1 gene rs3817198 polymorphism and breast cancer in the overall analysis, population-based studies, and European and American and African population only in the dominant genetic model. Results on analysis of recessive genetic model showed no relationship in overall and subgroup analysis.

Totally, two previous meta-analyses reported no association between LSP1 gene rs3817198 polymorphism and breast cancer [25-26]. This was while our analysis yielded significant association for the dominant genetic model. In subgroup analysis, a study conducted by Chen et al [25] indicated this association only in Caucasian for the recessive genetic model. Another study by Tang et al [26] revealed a significant association among Caucasian in both recessive and dominant genetic model. In our study, it was revealed that LSP1 gene rs3817198 polymorphism increased breast cancer risk in European and American and African population (Caucasian) for the dominant genetic model. Besides, the latter demonstrated no association in population -based or hospital-based studies, but this paper showed that in population-based studies LSP1 gene rs3817198 polymorphism is associated with increased breast cancer risk. These all is maybe because we included more studies.

This study had some limitations that may cause our results to be interfered cautiously. First, adjusted and unadjusted ORs were analyzed together. Second, we were not able to perform subgroup analysis for other risk factors of breast cancer, including menopausal status, dietary intake, obesity, and smoking. Third, data about per allele ORs was not collected in this study and per allele OR was not calculated.

Finally, it seems that LSP1 gene rs3817198 polymorphism is associated with breast cancer risk and this risk is more prominent in Caucasians. Nevertheless, further studies are required to confirm this association.

Table 2. Subgroup Meta-Analysis of Dominant and Recessive Genetic Model of LSP1 Rs3817198 Polymorphism and Breast Cancer Risk

Subgroup	Studies No.	Dominant		Recessive		P _h	I ₂	T ₂	Studies No.	P _h	I ₂	T ₂
		Fixed model OR (95% CI)	Random model OR (95% CI)	Fixed model OR (95% CI)	Random model OR (95% CI)							
Overall	13	1.07 (1.01-1.14)	1.07 (1.01-1.14)	0.98 (0.93-1.03)	1.10 (0.93-1.32)	0	63	0.05				
Control source												
Hospital based	3	1.02 (0.93-1.12)	1.02 (0.93-1.12)	0.95 (0.89-1.00)	0.88 (0.58-1.35)	0.41	0	3	0.13	51.3	0.08	
Population based	10	1.11 (1.02-1.20)	1.11 (1.02-1.20)	1.16 (1.02-1.33)	1.19 (0.96-1.48)	0.76	0	10	0.02	56.3	0.06	
Continent												
Europe_america_africa	7	1.10 (1.01-1.20)	1.10 (1.01-1.20)	1.22 (1.05-1.43)	1.20 (0.96-1.49)	0.53	0	7	0.11	42.6	0.03	
Asia	5	1.03 (0.94-1.13)	1.03 (0.94-1.13)	0.95 (0.89-1.00)	0.96 (0.71-1.30)	0.69	0	5	0.03	63.1	0.06	

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

Conflict of interest

The authors declared no conflict of interest

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